

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	MDL No. 2875
THIS DOCUMENT RELATES TO ALL CASES	HON. ROBERT B. KUGLER CIVIL NO. 19-2875 (RBK)

**CERTIFICATION OF ADAM M. SLATER IN SUPPORT OF PLAINTIFFS’
DAUBERT MOTION TO EXCLUDE TESTIMONY OF DANIEL CATENACCI, M.D.**

ADAM M. SLATER, hereby certify as follows:

1. I am an attorney at law within the State of New Jersey and a partner with the law firm of Mazie Slater Katz & Freeman, LLC, and serve as Plaintiffs’ Co-Lead Counsel. I am fully familiar with the facts and circumstances of these actions. I make this Certification in support of Plaintiffs’ motion to exclude the testimony of Daniel Catenacci, M.D.

2. Attached hereto as **Exhibit A** is a true and accurate copy of the September 13, 2021 Deposition Transcript of Daniel Catenacci.

3. Attached hereto as **Exhibit B** is a true and accurate copy of Daniel Catenacci’s August 27, 2021 Report.

4. Attached hereto as **Exhibit C** is a true and accurate copy of the September 14, 2021 Deposition Transcript of Daniel Catenacci.

5. Attached hereto as **Exhibit D** is a true and accurate copy of Adamson & Chabner, *The Finding of N-Nitrosodimethylamine in Common Medicines*, Oncologist. 2525:460-462 (2020).

6. Attached hereto as **Exhibit E** is a true and accurate copy of TEVA-MDL2875-00056962.

7. Attached hereto as **Exhibit F** is a true and accurate copy of an excerpt from Dr. Stephen M. Lagana's Expert Report.

8. Attached hereto as **Exhibit G** is a true and accurate copy of an excerpt from Dr. Mahya Etminan's Expert Report.

9. Attached hereto as **Exhibit H** is a true and accurate copy of an excerpt from Dr. Dipak Panigraphy's Expert Report.

10. Attached hereto as **Exhibit I** is a true and accurate copy of Archer & Michael, *Mechanisms of action of N-nitroso compounds*, CANCER SURVEYS 8, 241 (1989).

11. Attached hereto as **Exhibit J** is a true and accurate copy of Herron & Shank, *Methylated purines in human liver DNA after probable dimethylnitrosamine poisoning*, CANCER RESEARCH 40, 3116-3117 (1980).

12. Attached hereto as **Exhibit K** is a true and accurate copy of Liteplo & Meek, *Concise International Chemical Assessment Document 38 – N-Nitrosodimethylamine* (WHO 2002).

13. Attached hereto as **Exhibit L** is a true and accurate copy of Pottegård, Kristensen, Ernst, Johansen, Quartarolo, & Hallas, *Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study*, B.M.J. 12, 362 (Sept. 2018).

14. Attached hereto as **Exhibit M** is a true and accurate copy of Gomm, Röthlein, Schüssel, Brückner, Schröder, Heß, Frötschl, Broich, & Haenisch, *N-Nitrosodimethylamine-Contaminated Valsartan and the Risk of Cancer: A Longitudinal Cohort Study Based on German Health Insurance Data*, DEUTSCHES AERZTEBLATT INTERNATIONAL 118, 357-62 (2021).

15. Attached hereto as **Exhibit N** is a true and accurate copy of Anderson, Souliotis, Chhabra, Moskal, Harbaugh, and Kyrtopoulos, *N-nitrosodimethylamine-derived O(6)-methylguanine in DNA of monkey gastrointestinal and urogenital organs and enhancement by ethanol*, Int. J. Cancer 66, 130-4 (Mar. 1996).

16. Attached hereto as **Exhibit O** is a true and accurate copy of *Player v. Motiva Enterprises LLC*, No. Civ. 02–3216(RBK), 2006 WL 166452 (D.N.J. January 20, 2006).

17. Attached hereto as **Exhibit P** is a true and accurate copy of FDA, *FDA presents interim limits of nitrosamines in currently marketed ARBs* (Dec. 19, 2018), <https://tinyurl.com/4rkpdf5h>.

18. Attached hereto as **Exhibit Q** is a true and accurate copy of EPA, *N-Nitrosodimethylamine*, <https://tinyurl.com/9krh69u9>.

19. Attached hereto as **Exhibit R** is a true and accurate copy of EPA, *N-Nitrosodiethylamine*, <https://tinyurl.com/48y7nejw>.

20. Attached hereto as **Exhibit S** is a true and accurate copy of the relevant excerpt of the USP, Summary, Highlights and Timeline of General Chapter <1469> Nitrosamine Impurities (July 20, 2018).

21. Attached hereto as **Exhibit T** is a true and accurate copy of SOLCO00024226 (ZHP 129).

MAZIE SLATER KATZ & FREEMAN, LLC
Attorneys for Plaintiffs

By: /s/ Adam M. Slater

Dated: November 1, 2021

Exhibit A

1 UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY
2
3 IN RE: VALSARTAN, LOSARTAN,)
AND IRBESARTAN PRODUCTS)
4 LIABILITY LITIGATION)
_____) MDL No. 2875
5)
THIS DOCUMENT RELATES TO ALL)
6 CASES)

7
8
9 CONFIDENTIAL INFORMATION - SUBJECT TO PROTECTIVE ORDER
10
11

VIDEO DEPOSITION OF DANIEL CATENACCI, M.D.
12 VIA VIDEOCONFERENCE
13 September 13, 2021
9:20 a.m.

14
Volume 1

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16
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18 Reporter: John Arndt, CSR, CCR, RDR, CRR
19 CSR No. 084-004605
CCR No. 1186
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22
23
24

<p style="text-align: right;">Page 2</p> <p>1 DEPOSITION OF DANIEL CATENACCI, M.D., 2 produced, sworn, and examined via videoconference on 3 September 13, 2021, in the City of Chicago, State of 4 Illinois, before John Arndt, a Certified Shorthand 5 Reporter and Certified Court Reporter. 6 7 APPEARANCES OF COUNSEL 8 (All present via videoconference) 9 10 On Behalf of Plaintiffs: 11 Mazie Slater Katz & Freeman, LLC 12 103 Eisenhower Parkway, 2nd Floor 13 Roseland, NJ 07068 14 (973) 228-9898 15 BY: ADAM M. SLATER 16 aslater@mazieslater.com 17 JULIA S. SLATER 18 jslater@mazieslater.com 19 CHRISTOPHER J. GEDDIS 20 Morgan Law Firm, Ltd. 21 55 W. Wacker Drive, 9th Floor 22 Chicago, IL 60601 23 (312) 327-3386 24 BY: SCOTT A. MORGAN Levin Papantonio Rafferty 316 South Baylen Street Pensacola, FL 32502 (850) 435-7013 BY: DANIEL NIGH dnigh@levinlaw.com Martin, Harding & Mazzotti LLP PO Box 15141 Albany, NY 12212 (518) 724-2207 BY: ROSEMARIE RIDDELL BOGDAN rosemarie.bogdan@1800law1010.com Kanner & Whiteley, L.L.C. 701 Camp Street New Orleans, LA 70130 (504) 524-5777 BY: LAYNE HILTON</p>	<p style="text-align: right;">Page 4</p> <p>1 APPEARANCES OF COUNSEL (CONTINUED) 2 3 On Behalf of Sciegen Pharmaceutical and H.J. Harkins 4 d/b/a Pharma Pac: Hinshaw & Culbertson LLP 53 State Street, 27th Floor Boston, MA 02109 (617) 213-7045 BY: GEOFFREY M. COAN gcoan@hinshawlaw.com 6 On Behalf of CVS and Rite Aid: Barnes & Thornburg LLP 11 S. Meridian Street Indianapolis, IN 46204 (317) 231-6491 BY: KARA M. KAPKE kara.kapke@btlaw.com 7 On Behalf of Diane Washington, Personal Representative Of the Estate of Allen Washington: Schefman & Associates, PC 40900 Woodward Ave. Suite 111 Bloomfield Hills, MI 48304 (248) 594-2600 BY: BRYAN SCHEFMAN bryan@schefmanlaw.com 15 16 On Behalf of Albertson's LLC: Buchanan Ingersoll & Rooney PC 227 West Trade Street, Suite 600 Charlotte, NC 28202 (704) 444-3475 BY: CHRISTOPHER B. HENRY christopher.henry@bipc.com 19 20 On Behalf of Zhejiang Huahai Pharmaceutical Co., Ltd., Princeton Pharmaceutical Inc., Huahai U.S. Inc., and Solco Healthcare U.S., LLC: Duane Morris LLP 100 High Street, Suite 2400 Boston, MA 02110 (857) 488-4267 BY: LAUREN A. APPEL laappel@duanemorris.com 24</p>
<p style="text-align: right;">Page 3</p> <p>1 APPEARANCES OF COUNSEL (CONTINUED) 2 3 On Behalf of Teva: Greenberg Traurig, LLP One International Place, Suite 2000 Boston, MA 02110 (617) 310.6231 BY: NICHOLAS A. INSOGNA insognan@gtlaw.com 6 7 Greenberg Traurig, LLP 4 Embarcadero Center, Suite 3000 San Francisco, CA 94111 (415) 655-1285 BY: KATE WITTLAKE wittlakek@gtlaw.com 10 Greenberg Traurig, LLP 3333 Piedmont Road NE, Suite 2500 Atlanta, GA 30305 (678) 553-2103 BY: VICTORIA DAVIS LOCKARD lockardv@gtlaw.com 13 14 Pietragallo Gordon Alfano Bosick & Raspanti, LLP One Oxford Centre 301 Grant Street, 38th Floor Pittsburgh, PA 15219 (412) 263-1816 BY: CLEM C. TRISCHLER cct@pietragallo.com 17 18 Walsh Pizzi O'Reilly Falanga LLP 100 Mulberry Street, 15th Floor Newark, NJ 07102 (973) 757-1100 BY: LIZA M. WALSH lwalsh@walsh.law 21 22 23 24</p>	<p style="text-align: right;">Page 5</p> <p>1 APPEARANCES OF COUNSEL (CONTINUED) 2 3 For Aurobindo Pharma Ltd., Aurolife Pharma LLC, 4 and Aurobindo Pharma USA, Inc.: Cipriani & Werner, P.C. 450 Sentry Parkway, Suite 200 Blue Bell, PA 19422 (610) 862-1929 BY: JESSICA M. HEINZ jheinz@c-wlaw.com 7 8 Also present: 9 Elena Williams (Associate Litigation Counsel at 10 Viatrix) Michael Newell (videographer) 11 12 13 14 15 16 17 18 19 20 21 22 23 24</p>

<p style="text-align: right;">Page 6</p> <p>1 INDEX OF INTERROGATION 2 Examination by Mr. Slater Page 9 3 4 INDEX OF EXHIBITS 5 Exhibit 1 Page 11 6 (Notice to take videotaped 7 oral deposition) 8 Exhibit 2 Page 14 9 (Defendants Inc.'s responses and 10 Objections to plaintiffs' notice 11 Of videotaped deposition of Daniel 12 Catenacci, M.D.) 13 Exhibit 3 Page 28 14 (06/15/21 billing letter) 15 Exhibit 4 Page 31 16 (08/02/21 billing letter) 17 Exhibit 5 Page 38 18 (08/02/21 Catenacci report) 19 Exhibit 6 Page 41 20 (Amended list of materials considered) 21 Exhibit 7 Page 44 22 (08/27/21 Catenacci report) 23 Exhibit 8 Page 70 24 (Curriculum vitae) Exhibit 9 Page 70 (Fee schedule)</p>	<p style="text-align: right;">Page 8</p> <p>1 THE VIDEOGRAPHER: We are now on the 2 record. My name is Michael Newell. I'm a videographer 3 for Golkow Litigation Services. Today's date is 4 September 13, 2021. The time is 9:20 AM. This remote 5 video deposition is being held in the matter of in re 6 Valsartan, Losartan, and Irbesartan products liability 7 litigation for the U.S. District Court, District of New 8 Jersey. The deponent today is Daniel Catenacci, M.D. 9 All parties to this deposition are 10 appearing remotely and have agreed to the witness being 11 sworn in remotely. 12 Due to the nature of remote reporting, 13 please pause briefly before speaking to ensure all 14 parties are heard completely. 15 Will counsel please identify themselves 16 for the record? 17 MR. SLATER: Adam Slater for the 18 plaintiffs. 19 MR. INSOGNA: Nick Insogna, Greenberg 20 Traurig, for the defendants. Also in the room with me 21 are Clem Trischler for defendants and Kate Wittlake for 22 defendants, and also Scott Morgan for plaintiffs. 23 MR. SLATER: Okay. 24 THE VIDEOGRAPHER: Okay. The court</p>
<p style="text-align: right;">Page 7</p> <p>1 INDEX OF EXHIBITS (CONTINUED) 2 Exhibit 10 Page 70 3 (Prior testimony list) 4 Exhibit 11 Page 91 5 (Updated amended list of 6 Materials considered) 7 Exhibit 12 Page 154 8 (2012 Geynisman article) 9 (All exhibits are attached.) 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24</p>	<p style="text-align: right;">Page 9</p> <p>1 reporter today is John Arndt and will now swear in the 2 witness 3 4 The witness, DANIEL CATENACCI, M.D., first 5 having been duly sworn, testified as follows: 6 EXAMINATION 7 BY MR. SLATER: 8 Q. Good morning, Dr. Catenacci. 9 A. Good morning. 10 Q. I'm Adam Slater. I'm going to take your 11 deposition now in this litigation. You understand 12 that's the purpose of this proceeding; correct? 13 A. Yes. 14 Q. You understand you must tell the truth in 15 response to every question I ask you? 16 A. Yes. 17 Q. If I ask you a question that for some 18 reason is unclear to you or for any reason you don't 19 think you can answer it truthfully and completely 20 because of some question about what I'm asking, just 21 tell me. You can tell me the question's not clear. We 22 can specify what it is and I'll try to reask the 23 question if necessary. Okay? 24 A. Okay.</p>

Page 10	Page 12
<p>1 Q. Attorneys may object during the course of 2 the deposition. I think you've been through some, but 3 I'll just let you know or remind you that lawyers are 4 allowed to object. They're preserving their right for 5 the future.</p> <p>6 It's never, ever supposed to be a signal 7 to you for how to answer, so I would assume that's not 8 going to be happening, obviously, but don't be thrown 9 off by objections or discussions by counsel. And I 10 would assume, unless there's a very, very narrow 11 exception, you will be told to go ahead and answer the 12 question after an objection is placed. Okay?</p> <p>13 A. Okay.</p> <p>14 Q. Did you prepare for this deposition?</p> <p>15 A. Yes.</p> <p>16 Q. When did you first start preparing for the 17 deposition?</p> <p>18 A. Essentially I guess I started preparing 19 when I started reading about the topic in general. But 20 certainly after my report I knew that there was going 21 to be a deposition that would have told me which -- we 22 were deciding on which date. So during that time I 23 continued my reading. I was always reading and 24 continuing to get a broader understanding of the topic.</p>	<p>1 screen.</p> <p>2 MR. INSOGNA: If you could put it on the 3 screen, that would be helpful.</p> <p>4 MR. SLATER: Okay. Go ahead, Chris.</p> <p>5 BY MR. SLATER:</p> <p>6 Q. Doctor, Exhibit 1 is the notice to take 7 your deposition. Have you seen that document before?</p> <p>8 A. Yes.</p> <p>9 Q. Did you read the entire notice?</p> <p>10 A. Not in great detail.</p> <p>11 Q. Well, did you read the notice? Did you 12 read each of the categories of document requests?</p> <p>13 A. Yeah, I looked through the -- I looked 14 through it, yes.</p> <p>15 Q. Did you make any effort to locate and 16 produce any of the documents requested in the 17 deposition notice?</p> <p>18 A. I did not do that myself.</p> <p>19 Q. With regard to documents that would have 20 been in your possession and control, as opposed to 21 something that the lawyers who retained you might have, 22 did you make any effort to look for those documents 23 that were requested?</p> <p>24 MR. INSOGNA: Object to form.</p>
Page 11	Page 13
<p>1 Q. You referred to the point in time when you 2 started reading about the topic in general. When was 3 that?</p> <p>4 A. It was after I was contacted to serve as 5 an expert on the case.</p> <p>6 Q. Am I correct in understanding that before 7 you were first contacted to potentially act as an 8 expert for the defense in this case, you were not 9 reading up on the issues that are specific to this 10 report that you've written?</p> <p>11 A. That's correct.</p> <p>12 Q. And for example, you weren't following the 13 issue of nitrosamines in valsartan before you were 14 contacted?</p> <p>15 A. I heard of it. I heard of other stories 16 along that line, but I didn't focus on this in any 17 in-depth manner.</p> <p>18 Q. Let's put up -- well, rephrase. Let's 19 identify for the record Exhibit 1, which will be the 20 notice to take deposition.</p> <p>21 [Exhibit 1 marked for identification.]</p> <p>22 BY MR. SLATER:</p> <p>23 Q. And I don't know if you have that in the 24 room. If you do, we don't have to put it on the</p>	<p>1 A. I didn't need to because I had looked at 2 the documents that were produced that was comprehensive 3 for my whole report and all of my reliance list -- all 4 the documents that I reviewed.</p> <p>5 BY MR. SLATER:</p> <p>6 Q. And I neglected to say something at the 7 start that I had discussed with defense counsel prior, 8 so this is a little bit of a tangent. We have an 9 agreement and understanding that I will not be 10 addressing any liability opinions or medical 11 monitoring/medical surveillance opinions in this 12 deposition. I just wanted to put that on the record so 13 there wouldn't be a question later.</p> <p>14 MR. INSOGNA: And as I said before we got 15 started, we've traded some e-mails on that. We've not 16 delineated what subjects in your understanding fall 17 within the scope of that, but I understand that the 18 medical monitoring claim is not at issue at this point, 19 and I understand that you don't intend to ask questions 20 about it.</p> <p>21 MR. SLATER: Right. I don't intend to ask 22 questions about opinions or discussion about the 23 liability -- for example, how it occurred or whether it 24 should have occurred -- meaning the contamination of</p>

<p style="text-align: right;">Page 14</p> <p>1 the valsartan -- or the opinions provided as to whether 2 or to what extent medical monitoring or medical 3 surveillance would be appropriate in this case. 4 Hopefully that little bit of clarity will answer any 5 questions. 6 MR. INSOGNA: And as I said, yeah, we've 7 traded e-mails on that subject. We've not delineated 8 it, but I appreciate your -- what you said. 9 MR. SLATER: Okay. Thank you. 10 BY MR. SLATER: 11 Q. Okay, Doctor. Let's take down the 12 deposition notice, and let's go to Exhibit 2, which is 13 going to be the responses and objections we received to 14 the deposition notice. Thanks. 15 [Exhibit 2 marked for identification.] 16 MR. INSOGNA: I'm going to provide to Dr. 17 Catenacci. 18 MR. SLATER: Oh, perfect. If the doctor 19 has it in front of him, we don't have to have it on the 20 screen, then. Okay. 21 BY MR. SLATER: 22 Q. Doctor, looking now at Exhibit 2, which is 23 titled Defendant's I-N-C.'s responses and objections to 24 plaintiffs' notice of videotaped deposition of Daniel</p>	<p style="text-align: right;">Page 16</p> <p>1 Q. Number 3 asked for any notes or other 2 documentation, including PowerPoints for any 3 presentations, seminars, or classes given by Dr. 4 Catenacci with regard to the risks and benefits of any 5 angiotensin II receptor blockers or nitrosamines. 6 Do any such documents exist? 7 A. No. 8 Q. Is that because you have not given any 9 presentations, seminars, or classes regarding the risks 10 and benefits of angiotensin II receptor blockers or 11 nitrosamines? 12 A. Yes. 13 Q. Number 4, which is on Page 4, asked for 14 copies of any documents or articles relied upon for the 15 opinions set forth in the report served, if not listed, 16 in the report. 17 Are there any such documents or articles 18 that you've relied on that you didn't list somewhere in 19 the report? 20 A. No. 21 Q. And we're going to obviously -- rephrase. 22 We're going to come back to this, but there's been a 23 few different versions of the report, so when I'm 24 talking about the report, I'm talking about the most</p>
<p style="text-align: right;">Page 15</p> <p>1 Catenacci, M.D. 2 Do you see that? 3 A. Yes. 4 BY MR. SLATER: 5 Q. Have you seen this document before? 6 A. Yes, it was provided to me. 7 Q. Did you read the document? 8 A. I looked through it, similar to the other 9 ones. 10 Q. If you could turn to Page 2. There's a 11 heading that says objections to document requests, and 12 Number 1 was a request for various invoices. 13 Did you obtain and produce the invoices 14 that were requested? 15 MR. INSOGNA: Object to form. 16 A. I provided my invoice to counsel. 17 BY MR. SLATER: 18 Q. We'll come back to the invoice in a few 19 moments. Request Number 2, which is on Page 3, asked 20 for notes for any work that was not documented in the 21 invoices. 22 Is there any such documentation that you 23 would have possessed? 24 A. Not that I'm aware of.</p>	<p style="text-align: right;">Page 17</p> <p>1 up-to-date version, so -- you understood that? 2 A. Yes. 3 Q. Looking at Request Number 5 on Page 4. 4 Copies of any documents or articles reviewed in 5 connection with the report served, whether or not 6 listed in the report or attachments thereto. 7 Does any such document exist? 8 A. I think there would be many documents that 9 would fall into that category that I looked at that I 10 didn't include or reference. 11 Q. But they haven't been produced to us, to 12 your knowledge; correct? 13 MR. INSOGNA: Object to form. 14 BY MR. SLATER: 15 Q. Well, let me ask the question more 16 directly. To your knowledge, have any documents or 17 articles that you reviewed in connection with the 18 report that are not actually listed in the report or 19 the attachments to the report have been produced to us? 20 A. I'm not aware of that. 21 Q. Number 6 on Page 5 -- any illustrations, 22 PowerPoints, images, charts, tables, or demonstrative 23 exhibits that may be used by or with Dr. Catenacci in 24 connection with the Daubert hearing or trial testimony</p>

<p style="text-align: right;">Page 18</p> <p>1 in this litigation.</p> <p>2 Do you have any such -- rephrase. Do you</p> <p>3 have any such documentation that you've produced?</p> <p>4 A. No.</p> <p>5 Q. Number 7 -- well, let me ask you this,</p> <p>6 going back to 6. Is there any such documentation that</p> <p>7 you have not produced, meaning that you have it but you</p> <p>8 haven't produced it?</p> <p>9 A. No.</p> <p>10 Q. Number 7. Documentation of any research</p> <p>11 grant the witness has been provided to study any</p> <p>12 angiotensin II receptor blockers or nitrosamines or</p> <p>13 health effects potentially related thereto.</p> <p>14 Does any such documentation exist?</p> <p>15 A. No.</p> <p>16 Q. Is that because you've done no such</p> <p>17 research or study?</p> <p>18 A. That's correct.</p> <p>19 Q. Number 8 on Page 6. Documentation of any</p> <p>20 research the witness has performed with regard to any</p> <p>21 angiotensin II receptor blockers or nitrosamines or</p> <p>22 health effects potentially related thereto.</p> <p>23 I don't believe any such documentation has</p> <p>24 been produced. Is that because you have not performed</p>	<p style="text-align: right;">Page 20</p> <p>1 drugs?</p> <p>2 MR. INSOGNA: Object to form.</p> <p>3 A. I did not.</p> <p>4 BY MR. SLATER:</p> <p>5 Q. Were you asked to obtain such documents?</p> <p>6 A. I was not.</p> <p>7 Q. Number 10 requested any documents or other</p> <p>8 communications the witness has received from any person</p> <p>9 or entity with regard to nitrosamine impurities in any</p> <p>10 angiotensin II receptor blocker or other drug outside</p> <p>11 of information provided by counsel who retained the</p> <p>12 witness.</p> <p>13 So do any such documents or communications</p> <p>14 exist, to your knowledge?</p> <p>15 A. Everything that has been disclosed was</p> <p>16 provided.</p> <p>17 Q. By counsel?</p> <p>18 A. Yes.</p> <p>19 Q. And Number 11 requested any communications</p> <p>20 from the witness to any person or entity with regard to</p> <p>21 nitrosamine impurities in any angiotensin II receptor</p> <p>22 blocker or other drug outside of communications to</p> <p>23 counsel who retained the witness.</p> <p>24 Do any such communications exist?</p>
<p style="text-align: right;">Page 19</p> <p>1 any such research?</p> <p>2 MR. INSOGNA: Object to form.</p> <p>3 A. Yes.</p> <p>4 BY MR. SLATER:</p> <p>5 Q. Number 9 requested copies of any documents</p> <p>6 including protocols or information about the medication</p> <p>7 side effects available to the witness from any hospital</p> <p>8 or academic institution where he has worked, had an</p> <p>9 appointment or had privileges, which set forth</p> <p>10 information related to the risks and benefits of any</p> <p>11 angiotensin II receptor blocker or nitrosamine.</p> <p>12 First of all, did you attempt to identify</p> <p>13 any such documents to produce to us?</p> <p>14 A. No.</p> <p>15 Q. Do you know if such documents exist, for</p> <p>16 example, at the institutions you work at currently?</p> <p>17 A. I do not.</p> <p>18 Q. For example, there might -- rephrase. I</p> <p>19 would think the hospital that you work at there's a</p> <p>20 formulary and that there would be lists of the</p> <p>21 different medications, including their risks and</p> <p>22 benefits.</p> <p>23 Did you consult that at all regarding any</p> <p>24 of the drugs that are at issue here -- the valsartan</p>	<p style="text-align: right;">Page 21</p> <p>1 A. Anything that's been disclosed has been</p> <p>2 provided.</p> <p>3 Q. Outside of documented communications, for</p> <p>4 example, in an e-mail or a letter, have you had any</p> <p>5 such oral communications with anybody other than</p> <p>6 counsel about the nitrosamine impurities in the</p> <p>7 angiotensin II receptor blockers?</p> <p>8 A. No.</p> <p>9 Q. Have you discussed the subject matter of</p> <p>10 this litigation or the report you wrote in this</p> <p>11 litigation with anybody other than counsel?</p> <p>12 THE REPORTER: I'm sorry. Was there an</p> <p>13 answer?</p> <p>14 A. No.</p> <p>15 BY MR. SLATER:</p> <p>16 Q. Finally, Number 12 requested any textbook</p> <p>17 referenced by the witness in forming his opinions.</p> <p>18 Are there any such textbooks?</p> <p>19 A. No. Other -- sorry.</p> <p>20 MR. INSOGNA: Are you asking other than</p> <p>21 what's listed on the reliance list?</p> <p>22 BY MR. SLATER:</p> <p>23 Q. Well, no, my question is, first of all --</p> <p>24 well, yeah. Let me phrase it. To the extent that a</p>

<p style="text-align: right;">Page 22</p> <p>1 textbook was referenced in the report as having been 2 relied on, were those produced? 3 MR. INSOGNA: And counsel, I would just 4 note our objection to things that the witness had only 5 in hard copy form. 6 MR. SLATER: Well, I just want to -- we 7 can talk through what the logistics would have been. I 8 just want to find out what was or wasn't done, and then 9 we can talk through. I don't think there's anything to 10 object to yet. 11 BY MR. SLATER: 12 Q. My just question, Doctor, is this. Did 13 you -- well, first of all, let's ask this. I've read 14 your report, but let's state for the record. 15 Did you actually rely on any textbook to 16 form your opinions that are set forth in your report? 17 A. No. Most of the -- all the references 18 that I use are journal articles. They're not textbooks 19 per se. 20 Q. Okay, we can put the -- you can put aside 21 that response to deposition notice. I'm hopeful -- 22 well, actually, we'll get to that. We'll find out what 23 I'm hopeful about later, and we'll talk about it during 24 lunch or something.</p>	<p style="text-align: right;">Page 24</p> <p>1 A. Yes. I think it's Alexandra, maybe. 2 Q. I want to get that accurate, so I 3 apologize if I misstated. When you were contacted in 4 March of 2021, what was your understanding as to what 5 you were being asked if you were willing to do? Let me 6 ask it differently. 7 When you were first contacted in March 8 2021, what was your understanding as to what you were 9 being asked to do? 10 A. I was being asked to familiarize myself 11 with the issue at hand and ultimately be able to 12 provide a number of different things in a report 13 ultimately, which was first starting with a general 14 background of what is cancer, carcinogenesis, and with 15 a focus on risk factors and focusing on some specific 16 cancers that were listed in the litigation, to provide 17 statistics in terms of incidences of these cancers and 18 cancers overall, and then to evaluate whether or not 19 ultimately the question at hand -- which was the 20 impurities of NDMA and NDEA -- whether or not they 21 would lead to an increased risk over standard rates of 22 cancer. 23 Another thing they asked was whether or 24 not putative exposures to these agents would lead to</p>
<p style="text-align: right;">Page 23</p> <p>1 When were you first contacted by anybody 2 with regard to this litigation? 3 A. I think it was back in March of this year. 4 Q. March of 2021? 5 A. Yes. 6 Q. Who contacted you? 7 A. Alex Lagos. 8 Q. Who is Alex Lagos? 9 A. He's a counsel for Greenberg Traurig. 10 Q. An attorney at Greenberg Traurig? 11 A. Yes. 12 Q. Do you know how -- rephrase. Do you know 13 why Alex Lagos contacted you, as opposed to somebody 14 else? Do you know how he got to you? 15 A. I looked back at that e-mail, and she 16 indicated that another doctor who I know in Miami had 17 referred her to me. 18 Q. Who was that doctor in Miami? 19 A. Greg Lockhart (ph). 20 Q. Greg Lockhart? What type of physician is 21 Greg Lockhart? 22 A. Same as me. He's a GI medical oncologist. 23 Q. And I think when I said Alex Lagos, I 24 think I said he but you said she. So did I misstate?</p>	<p style="text-align: right;">Page 25</p> <p>1 the need to monitor patient -- people or patients that 2 had these exposures and do anything different than what 3 would be routine surveillance over time. 4 Q. Did you have an understanding as to who 5 was retaining you when you actually agreed to go 6 forward as an expert in this case? 7 A. Yes, I think I was made clear that they 8 were counsel for the defense of this -- of one of the 9 pharmaceutical companies that was involved, which I 10 believe was Teva. 11 Q. So you understood -- I'm sorry. I didn't 12 mean to interrupt. 13 A. And so the answer to your question is, 14 yes, I knew that that was where they were coming from. 15 Q. So you understood that you were being 16 retained by attorneys from Greenberg Traurig to be an 17 expert on behalf of Teva in this litigation? 18 MR. INSOGNA: Object to form. 19 A. Yes, that's what my understanding was. 20 BY MR. SLATER: 21 Q. Other than Alex Lagos, have you spoken to 22 any other attorneys in connection with this litigation? 23 A. Yes. 24 Q. Who else have you spoken with?</p>

<p style="text-align: right;">Page 26</p> <p>1 A. Nick Insogna. Katie -- forgive me -- last 2 name. I don't have all the names.</p> <p>3 Q. Well, what I want to know is the names 4 that you can recall.</p> <p>5 You told me Katie, who's present at the 6 deposition; right?</p> <p>7 A. Yes.</p> <p>8 Q. Had you ever spoken to her before today?</p> <p>9 A. Yes.</p> <p>10 Q. When did you first speak to Katie?</p> <p>11 A. I don't know exactly, but it was often in 12 calls along with Nick.</p> <p>13 Q. Do you know what law firm Katie works 14 with?</p> <p>15 A. I believe the same law firm.</p> <p>16 Q. What other attorneys, if any, have you 17 spoken with about this case or your report?</p> <p>18 A. There was a couple of other attorneys, I 19 believe, from other defendants, the names of which I 20 didn't memorize and I don't know. But that was during 21 a call that we had on Saturday, and also a meeting on 22 Wednesday.</p> <p>23 Q. When you refer to a call on Saturday, 24 you're talking about two days ago?</p>	<p style="text-align: right;">Page 28</p> <p>1 you do recall who you've spoken to about this case or 2 your report?</p> <p>3 A. Outside of what I just mentioned, no.</p> <p>4 MR. SLATER: Chris, if we have Dr. 5 Catenacci's invoice, I'd like to put that up on the 6 screen, please -- or invoices.</p> <p>7 BY MR. SLATER:</p> <p>8 Q. Great. Doctor, on the screen we have what 9 we're marking as Exhibit 3 to your deposition, which 10 is --</p> <p>11 [Exhibit 3 marked for identification.]</p> <p>12 MR. INSOGNA: Adam, we don't have that up 13 on the screen.</p> <p>14 MR. SLATER: You don't have it on the 15 screen?</p> <p>16 MR. INSOGNA: I'm not showing it, no.</p> <p>17 MR. SLATER: I'm looking at it on the 18 screen.</p> <p>19 MR. INSOGNA: I see it. I see it. Yes.</p> <p>20 MR. SLATER: Okay. I'll start over.</p> <p>21 BY MR. SLATER:</p> <p>22 Q. In front of you is what we've marked as 23 Exhibit 3, which is our under -- rephrase. On the 24 screen we have Exhibit 3, a June 15, 2021, letter, that</p>
<p style="text-align: right;">Page 27</p> <p>1 A. Yes.</p> <p>2 Q. And when you refer to a meeting on 3 Wednesday, are you talking about last Wednesday, about 4 five days ago? Other than the two calls that -- well, 5 rephrase.</p> <p>6 The meeting last Wednesday -- was that 7 also a call, or was that in person?</p> <p>8 A. That was on site here in person, but the 9 attorneys that I mentioned from other defendants were 10 on Zoom.</p> <p>11 Q. Do you know who from other defendants 12 attended -- what lawyers attended on Wednesday of last 13 week?</p> <p>14 A. I don't have the names.</p> <p>15 Q. Do you know who in terms of lawyers for 16 other defendants attended the call on Saturday, two 17 days ago?</p> <p>18 A. Same -- the same attorneys.</p> <p>19 Q. I think Clem Trischler -- Clem is in the 20 room -- rephrase.</p> <p>21 I believe Clem Trischler is present. Had 22 you ever spoken with him before today?</p> <p>23 A. No, not that I'm aware of.</p> <p>24 Q. Are there any other attorneys whose names</p>	<p style="text-align: right;">Page 29</p> <p>1 you wrote to Alex Lagos.</p> <p>2 What is that document?</p> <p>3 A. That looks like it's the first invoice 4 that I submitted for this work.</p> <p>5 MR. SLATER: Chris, can you blow up that 6 front page a little bit, please, so I can read it?</p> <p>7 Perfect. That's good.</p> <p>8 BY MR. SLATER:</p> <p>9 Q. This states that as of June 15, 2021, you 10 had spent 19 hours at \$700 an hour and the total was 11 \$13,300; correct?</p> <p>12 A. Yes.</p> <p>13 MR. SLATER: And Chris, can you scroll 14 down to the next page? I want to see what other 15 information's attached, please.</p> <p>16 MR. GEDDIS: What page? Adam, can you 17 hear me?</p> <p>18 MR. SLATER: I would like to get the 19 actual invoices, too, or did we only get the cover 20 letter?</p> <p>21 MR. GEDDIS: I think that's --</p> <p>22 MR. SLATER: I can't hear you, Chris.</p> <p>23 MR. GEDDIS: Adam, it's only one page. I 24 don't think there's -- I don't know if there's an</p>

<p style="text-align: right;">Page 30</p> <p>1 additional --</p> <p>2 MR. SLATER: Okay, let me go back into it</p> <p>3 then. All right. You can scroll down a little more so</p> <p>4 we can see the body of the document again. Can you</p> <p>5 blow it up to where it was? Okay.</p> <p>6 BY MR. SLATER:</p> <p>7 Q. Doctor, was there any enclosure to this</p> <p>8 letter, or was this simply your -- this -- rephrase.</p> <p>9 Was there any enclosure, or was this</p> <p>10 letter your entire invoice?</p> <p>11 A. That is my entire invoice.</p> <p>12 Q. Do you keep records of the time that you</p> <p>13 have spent working on this case and what you were doing</p> <p>14 when you were spending time on this case so that if</p> <p>15 someone asked you for an itemized list of how you got</p> <p>16 to the 19 hours, that you would be able to provide</p> <p>17 that?</p> <p>18 A. I don't keep it written, no.</p> <p>19 Q. How did you know you spent 19 hours as of</p> <p>20 June 15? Was that an estimate?</p> <p>21 A. I looked back at the dates that I knew I</p> <p>22 was reviewing and reading and added time that I spent</p> <p>23 up writing, because this was also the draft report.</p> <p>24 Q. Between June 15, 2021, and today, which is</p>	<p style="text-align: right;">Page 32</p> <p>1 Is that your second invoice in this case?</p> <p>2 MR. INSOGNA: Speak up a little bit. My</p> <p>3 voice cracked.</p> <p>4 A. Yes.</p> <p>5 MR. SLATER: Chris, can you blow it up a</p> <p>6 little more, please? Okay.</p> <p>7 BY MR. SLATER:</p> <p>8 Q. According to this invoice, after your June</p> <p>9 15, 2021, invoice and up till August 2, 2021, you spent</p> <p>10 an additional 94.5 hours.</p> <p>11 Is that correct?</p> <p>12 A. Yes.</p> <p>13 Q. Did you keep any itemized notes or lists</p> <p>14 of what time you spent and what you did during those</p> <p>15 time blocks, or did you do what you told me earlier,</p> <p>16 which was you just went back to see when you worked on</p> <p>17 it and estimated?</p> <p>18 MR. INSOGNA: Object to form.</p> <p>19 A. The latter.</p> <p>20 BY MR. SLATER:</p> <p>21 Q. Is there any other invoice after August</p> <p>22 2nd?</p> <p>23 A. No, not yet.</p> <p>24 Q. How much time have you spent after the</p>
<p style="text-align: right;">Page 31</p> <p>1 September 13, 2021, how much additional time have you</p> <p>2 spent on this matter?</p> <p>3 MR. INSOGNA: Object to form.</p> <p>4 A. Depends which dates. Since this invoice?</p> <p>5 BY MR. SLATER:</p> <p>6 Q. Since the invoice and up to before we</p> <p>7 started this deposition today, how much additional time</p> <p>8 have you spent on this matter?</p> <p>9 A. There is a second invoice that has some of</p> <p>10 that time already documented, and that was up unto this</p> <p>11 submission of my report, and then since then I'd have</p> <p>12 to go back and calculate it.</p> <p>13 Q. Let's go now to the second invoice letter,</p> <p>14 which we'll mark as Exhibit 4.</p> <p>15 [Exhibit 4 marked for identification.]</p> <p>16 BY MR. SLATER:</p> <p>17 Q. On the screen we have Exhibit 4, which is</p> <p>18 in August.</p> <p>19 MR. SLATER: Can you scroll up to the</p> <p>20 date, please, Chris? Okay.</p> <p>21 BY MR. SLATER:</p> <p>22 Q. On the screen we have Exhibit 4, which is</p> <p>23 an August 2, 2021, letter that you sent to Nicholas</p> <p>24 Insogna at Greenberg Traurig.</p>	<p style="text-align: right;">Page 33</p> <p>1 August 2nd invoice was sent up until before we started</p> <p>2 the deposition on this case?</p> <p>3 A. Like I said, I'd have to go back and look</p> <p>4 at and calculate it.</p> <p>5 Q. Can you give me your best estimate of how</p> <p>6 much time you've spent between August 2, 2021, and</p> <p>7 today?</p> <p>8 A. Many hours.</p> <p>9 Q. Can you give me some sense of what you</p> <p>10 mean by that?</p> <p>11 A. I have to go back and look at the actual</p> <p>12 times that I spent on it.</p> <p>13 Q. So you have no -- you're not able to</p> <p>14 estimate in any way?</p> <p>15 MR. INSOGNA: Object to form.</p> <p>16 A. I'd have to go back and look at the actual</p> <p>17 times that I blocked off that I know, for example, and</p> <p>18 add them up, and I haven't done that yet. I was going</p> <p>19 to do it after this deposition.</p> <p>20 BY MR. SLATER:</p> <p>21 Q. In terms of actual preparation for the</p> <p>22 deposition, do you know how much time you've spent</p> <p>23 actually preparing for the deposition?</p> <p>24 I'm not talking about the general work</p>

<p style="text-align: right;">Page 34</p> <p>1 you've done on your report, but focused work to try to 2 prepare yourself for this proceeding. 3 MR. INSOGNA: Object to form. 4 A. Like I said earlier, it depends on the 5 definition of that, because I've been essentially 6 preparing for this since the get-go, but certainly 7 after the submission of the report when I knew that a 8 deposition was the next step, that was initially when I 9 started to really prepare, and then really focused 10 preparation in the last few weeks with more dedicated 11 time to it. 12 BY MR. SLATER: 13 Q. Working backwards, in the last few weeks, 14 can you estimate how much time you've spent preparing 15 for the deposition? 16 A. At least three to four hours a day, and in 17 some days more than that. Like, for example, the last 18 few weekends were basically doing it all day. 19 Q. And that's focused preparation for the 20 deposition? 21 MR. INSOGNA: Object to form. 22 A. Could you explain -- define what that 23 means? 24 BY MR. SLATER:</p>	<p style="text-align: right;">Page 36</p> <p>1 here; correct? 2 A. Not relying on them, no. 3 Q. Bear with me. I got to write something 4 down. 5 Have you seen the deposition of Dr. 6 Pennegrafe (ph)? 7 A. I have not. That was on Friday, I think. 8 Q. Okay, let's take down this invoice, 9 please. 10 Do you know how much time or can you 11 estimate how much time you've spent in actual 12 discussions or meetings with counsel as part of your 13 preparation for the deposition? 14 A. There was the three hours I mentioned on a 15 Zoom call on Saturday, the meeting in person here, 16 hybrid with Zoom on Wednesday, which I believe was five 17 or six hours. And then there were various calls. This 18 is just for the deposition preparation? 19 Q. Correct. 20 A. Yeah, then there were various short calls 21 on the phone that probably amounted to less than an 22 hour, an hour, approximately. 23 Q. In terms -- so rephrase. In terms of 24 actual meetings, whether in person or virtual or by</p>
<p style="text-align: right;">Page 35</p> <p>1 Q. What I mean is this. That's -- the time 2 you just described is time you've spent with the focus 3 on preparing for this deposition? 4 MR. INSOGNA: Same objection. 5 A. Meeting, having -- reviewing -- 6 re-reviewing things that I had read before, 7 re-reviewing my report, reviewing new information that 8 came along like the depositions of the expert 9 witnesses, et cetera, the -- all of the reports of the 10 defense that came out after I submitted my report. All 11 of that, I mean, I think, would qualify as preparing 12 for this December, and so yes, all of those hours. 13 BY MR. SLATER: 14 Q. You said reviewing the reports of all of 15 the defense experts. 16 Have you, to your knowledge, reviewed the 17 reports of all the defense experts? 18 A. I believe so, yes. 19 Q. Did you rely on those reports in any way 20 in forming the opinions that you're providing here, or 21 did you see them all after the fact? 22 A. I saw them all after the fact. 23 Q. So if I understand, you're not relying on 24 the other defense expert reports for your opinions</p>	<p style="text-align: right;">Page 37</p> <p>1 telephone, you're estimating about 10 hours for those 2 meetings? 3 A. Right. 4 Q. Do I understand that correctly? 5 A. And that's not e-mail communication. 6 Q. And I'm certainly not going to ask you for 7 the contents of any e-mails, but is it fair to say that 8 you've had many e-mail communications about and in 9 preparation for this deposition? 10 MR. INSOGNA: Object to form. 11 A. In various aspects of communication, yes. 12 BY MR. SLATER: 13 Q. What do you mean by "in various aspects of 14 communication"? 15 A. About the report, where to be for the 16 deposition, like logistics. All kinds of different 17 aspects regarding the deposition. 18 Q. And those aspects would include 19 substantive communications; correct? 20 MR. INSOGNA: Object to form. 21 A. Not usually. Most of those would be by 22 communication, in person or on the phone, or by Zoom. 23 MR. SLATER: All right, Chris. 24 BY MR. SLATER:</p>

<p style="text-align: right;">Page 38</p> <p>1 Q. If we could -- and I think you have the 2 reports there, Doctor. If you have your initial report 3 of August 2nd, 2021, that's the next exhibit I'd like 4 to go to. We'll mark that as Exhibit 5. 5 [Exhibit 5 marked for identification.] 6 MR. SLATER: And just logistically for our 7 end, I assume for Chris and the court reporter, we 8 still can mark that document as Exhibit 5 even if we 9 don't put it up on the screen; right? 10 MR. GEDDIS: That's producing (ph) it all 11 on mine. 12 MR. SLATER: I just want to make sure it's 13 being handled. That's all. I'm not going to get into 14 the details. I just want to make sure it didn't get 15 lost. Okay. 16 THE REPORTER: From my end, as long as he 17 puts it in the Dropbox, I'll mark it as an exhibit. 18 MR. SLATER: Terrific. 19 BY MR. SLATER: 20 Q. Okay, Doctor, do you have in front of you 21 x5, your August 2, 2021, report in this case? 22 A. I do. 23 Q. When you wrote this report, did you 24 attempt to set forth each of the opinions you had</p>	<p style="text-align: right;">Page 40</p> <p>1 Q. And before you signed the report, did you 2 carefully read it to make sure it said what you wanted 3 it to say? 4 A. Several times for substance and -- for the 5 substance particularly. The details and spelling and 6 things like this, to the best of my ability, although 7 even now when I read it every now and then I find a 8 typo. 9 Q. Before you signed the report, did you 10 ensure that the references that are found within the 11 report were accurate in the sense that if you put a 12 reference number, that it actually correlated to the 13 actual document that you meant to reference? 14 A. I tried to, yes. 15 Q. When you say you tried to, what does that 16 mean? 17 A. As you know, after I submitted the report, 18 it was noticed that some of the references got mixed 19 and that needed to be corrected, and hence the amended 20 report that corrected that. 21 Q. When you say the references got mixed, 22 what does that mean? 23 A. It means that they got referenced at the 24 wrong location within the text.</p>
<p style="text-align: right;">Page 39</p> <p>1 reached in this case? 2 A. Yes. 3 Q. And did you in fact set forth the opinions 4 you had reached in this case when you signed your 5 August 2, 2021, report? 6 THE REPORTER: I'm sorry. Did you answer? 7 A. Yes. 8 BY MR. SLATER: 9 Q. In the course of the report itself, you 10 talk about or speak to various facts that you obtained 11 either from studies or from documents that were 12 provided, et cetera. 13 Did you reference and discuss those facts 14 that were most important to you in forming your 15 opinions in the report? 16 MR. INSOGNA: Object to the form. 17 A. Yes. 18 BY MR. SLATER: 19 Q. When you wrote this report, did you write 20 it with care and precision? 21 A. To the best of my ability, yes. 22 Q. Did you choose the words that you used in 23 the report with care and precision? 24 A. Yes.</p>	<p style="text-align: right;">Page 41</p> <p>1 Q. Did you find any examples where you had 2 referenced an article for a proposition or something 3 you stated in the report and in fact you didn't intend 4 to reference any source? 5 A. Not that I'm aware of, no. 6 Q. In addition to the list of references that 7 are numbered, there's another list that we were 8 provided as an exhibit of materials considered. 9 Did you read all of the -- and we're going 10 to get to the specific document, but did you read all 11 of the articles or other documents that are listed on 12 your list of materials considered? Did you read every 13 single one of those documents that are listed? 14 A. Yes, to different amounts of detail and 15 different numbers of times. Some were more important 16 than others. 17 Q. Let's go now to the next exhibit, which is 18 going to be the August 25, 2021, report. 19 [Exhibit 6 marked for identification.] 20 MR. INSOGNA: Set that one aside so you 21 don't confuse them. Adam, when you say August 25, I 22 believe that's the one we told you to disregard and we 23 sent the August 27th report that Dr. Catenacci 24 provided.</p>

<p style="text-align: right;">Page 42</p> <p>1 MR. SLATER: Yeah, I just wanted to make 2 sure that I marked each of the documents that were 3 produced to us so I can ask him about them. I just 4 feel like I want to be -- I just need to be thorough to 5 make sure everything's identified and I get everything 6 in context. We're going to get to the August 27, but 7 I'm just going in order of what was served to us. 8 BY MR. SLATER: 9 Q. Doctor, do you have the -- oh, you're 10 getting it. Okay. 11 A. That's -- 12 MR. INSOGNA: Yeah. 13 BY MR. SLATER: 14 Q. Doctor, looking now at Exhibit 6, which is 15 the August 25, 2021, report we were provided. 16 Have you seen that report before? 17 A. Yes. 18 Q. And I see that your signature is at the 19 end of the report after Page 60. 20 Did you sign this document? 21 MR. INSOGNA: Object to form. (Inaudible) 22 document. 23 A. Looks like my signature's there, but it's 24 not actually -- my name is in there with my</p>	<p style="text-align: right;">Page 44</p> <p>1 report; correct? 2 A. No. 3 Q. And just to be clear, why was the August 4 25, 2021, report sent to us after we had been served 5 the August 2, 2021, report? 6 A. I believe it was to correct some of those 7 noted mistakes with the referencing. 8 Q. Was any change made to the substantive 9 content of the report? 10 A. No. 11 Q. Now let's go to the August 27, 2021, 12 report, which we'll mark as Exhibit 7. 13 [Exhibit 7 marked for identification.] 14 BY MR. SLATER: 15 Q. Do you have that in front of you? 16 A. Yes. 17 Q. Oh, I'm sorry. I'm sitting here waiting 18 for you to get it and you're waiting for me to realize 19 you had it. 20 A. This is the one we started with that I had 21 from the get-go. 22 Q. Looking now at Exhibit 6, the August 27, 23 2021, report. 24 To your knowledge, is that the most</p>
<p style="text-align: right;">Page 43</p> <p>1 credentials, but there's not an actual signature. 2 BY MR. SLATER: 3 Q. The version that you're looking at doesn't 4 have a signature on it? 5 A. August 25th on Page 47? 6 Q. Go further. If you go past Page 60, there 7 is a signature after Page 60. 8 A. I only have Page 60. That's where my 9 version ends that I have here in front of me. 10 Q. In looking at the signature on this 11 report, it seemed to look the same as the signature on 12 the prior version. It looks like an electronic 13 signature. 14 Is that accurate? 15 A. Yes. 16 Q. If you look at the very first page of the 17 August 25, 2021, report, the bottom left-hand column, 18 or bottom left of the page. 19 You see where it says active and then 20 there's a number after that? 21 A. Yes. 22 Q. Do you know what that refers to? 23 A. I do not. 24 Q. That's not something you placed on the</p>	<p style="text-align: right;">Page 45</p> <p>1 up-to-date version of the report and exhibits? 2 A. Yes. 3 Q. Was this version of the report provided 4 to, as you stated earlier, correct the mistakes with 5 the references? 6 A. Yes, I believe so. 7 Q. Now, it's my understanding that with the 8 exception of Exhibit B, which we'll get to -- well, let 9 me ask the question differently. Exhibit A to this 10 report, the August 27, 2021, report, is a CV. 11 Is that your current and up-to-date CV? 12 A. No, I have -- I usually update it monthly 13 pretty much, so I have Number 1 (ph). 14 Q. Is there anything that's been added to 15 this CV that relates in any way to the subject matter 16 of this litigation? 17 A. No. 18 Q. If you could, I'd like -- rephrase. I'd 19 like to walk through a little bit of your CV and ask 20 you a couple questions if we could, please. 21 A. Okay. 22 Q. Let's go, if we could, to Page 3. There's 23 a heading original articles. 24 A. Yes.</p>

<p style="text-align: right;">Page 46</p> <p>1 Q. Are those articles that you have authored 2 or coauthored? 3 A. Yes. 4 Q. And those are found in the peer-reviewed 5 literature, is my understanding? 6 A. Yes. 7 Q. Do any of your published articles that are 8 listed here address specifically any of the issues at 9 issue in this litigation? 10 MR. INSOGNA: Object to form. 11 A. No, not specifically. 12 BY MR. SLATER: 13 Q. I'm going to go through a few more 14 specific questions just to make sure we're all on the 15 same page. 16 Do any of these articles relate to or 17 discuss NDMA, NDEA, or nitrosamines in any way? 18 A. None of the original articles, no. 19 Q. Have you ever conducted or participated in 20 any way in a study regarding the health effects of NDMA 21 or NDEA or other nitrosamines? 22 A. No. 23 Q. Do you have any plans to conduct such a 24 study?</p>	<p style="text-align: right;">Page 48</p> <p>1 of those questions you asked. 2 Q. Go if you could to Page 9, please. 3 A. Okay. 4 Q. There's a heading consensus statements and 5 guidelines. 6 A. Yes. 7 Q. Do any of the materials listed under that 8 heading address any of the issues specific to this 9 litigation? 10 MR. INSOGNA: Object to form. 11 A. No. 12 BY MR. SLATER: 13 Q. For example, do any address nitrosamines 14 in any way? 15 A. No. 16 Q. Do any of them address the risks or 17 benefits of valsartan or similar drugs? 18 A. No. 19 Q. Looking now on Page 9 of the heading book 20 chapters. The same question. Do any of those address 21 the specific issues in this litigation? 22 MR. INSOGNA: Same objection. 23 A. No. 24 BY MR. SLATER:</p>
<p style="text-align: right;">Page 47</p> <p>1 A. No. 2 Q. Have you ever made a submission to an IRB, 3 an institutional review board, regarding such a study? 4 A. No. 5 Q. Have you -- rephrase. Do any of these 6 publications address in any way the risks and benefits 7 of valsartan or other drugs in that medication class? 8 A. No. 9 Q. Do any of your articles address causation 10 of cancer due to exposure to chemicals? 11 A. No original articles, no. 12 Q. When you say no original articles, I just 13 want to make sure you're not making a distinction to 14 something else. What do you -- so what do you mean by 15 that? 16 A. You had asked me at the beginning of this 17 line of questioning about where -- on Page 3 when it 18 was talking about original articles. But if you look 19 at further pages, there are other types of articles 20 that I would publish, and those include editorials, 21 commentaries, reviews of given topics, and consensus 22 statement and guidelines, book chapters, et cetera, so 23 none of the work that would be considered original work 24 where I'm doing actual new research has to do with any</p>	<p style="text-align: right;">Page 49</p> <p>1 Q. Do any of them address nitrosamines in any 2 way? 3 A. No. 4 Q. Do any of them address the risks and 5 benefits of medications like valsartan to treat 6 hypertension? 7 A. No. One thing I noticed on the book 8 chapters -- because I didn't realize that that's where 9 it was -- is Number 95. 10 Q. Okay. 11 A. Which is our society, the American Society 12 of Clinical Oncology, or ASCO -- A-S-C-O -- where I 13 co-wrote with my colleague this self-evaluation 14 program, which is how medical oncologists get certified 15 and get recertified, so this is the study manual. And 16 so in that encompasses all GI cancers, and so there are 17 background sections that may allude to risk factors and 18 other things that would come up with various cancers. 19 And so I think there would be probably 20 references that nitrosamines have been reported to be 21 associated with gastric cancer and that other reports 22 have shown the opposite and that there's no clear 23 consensus on those dietary studies. 24 Q. This was authored, it looks like, 2021; is</p>

<p style="text-align: right;">Page 50</p> <p>1 that correct?</p> <p>2 A. Yes. Yes.</p> <p>3 Q. Do you know when in 2021 you authored it?</p> <p>4 A. Well, this was a process over a year, and</p> <p>5 that they continually elicit us with updates for new</p> <p>6 trial outcomes and to add to the guidelines for</p> <p>7 treatment, so it's an ongoing process. I think it came</p> <p>8 online in the late spring, early summer, for people</p> <p>9 using it to study for their board exams.</p> <p>10 Q. As you did different iterations of that</p> <p>11 document, would you have been red-lining so that you</p> <p>12 could see each of the changes and be able to know when</p> <p>13 you were modifying the language as you went forward?</p> <p>14 A. I would be going back to the most recent</p> <p>15 version and adding to it and then resubmitting the</p> <p>16 change -- the new version of the document.</p> <p>17 Q. There's a second doctor listed there, B.N.</p> <p>18 Polite, or "polite"?</p> <p>19 A. "Polite," yeah.</p> <p>20 Q. Polite? Who is that?</p> <p>21 A. He's a colleague of mine at the</p> <p>22 university. He's also a GI medical oncologist.</p> <p>23 Q. Did Dr. Polite also contribute to the</p> <p>24 writing of this document?</p>	<p style="text-align: right;">Page 52</p> <p>1 MR. INSOGNA: Object to form.</p> <p>2 A. This particular self-evaluation program,</p> <p>3 no, actually wasn't published when I was talking to</p> <p>4 them mostly; right? But in my actual report and on my</p> <p>5 reliance list is a reference similar to that flavor,</p> <p>6 which is under the review section of my publication,</p> <p>7 which is Reference 80, which is -- was written by my</p> <p>8 fellow and -- which is a trainee -- and review articles</p> <p>9 are common to do like that, and that's the background</p> <p>10 on gastroesophageal cancer.</p> <p>11 And a similar reference is in there in</p> <p>12 terms of noting a number of potential associations with</p> <p>13 various cancers, with various gastroesophageal cancers,</p> <p>14 and pointing out that there are some that do and some</p> <p>15 that don't suggest an association of nitrosamines with</p> <p>16 stomach cancer.</p> <p>17 And that's in my report when I'm talking</p> <p>18 about risk factors for gastric cancer, and the dietary</p> <p>19 studies that are lower down in my report. I'm -- that.</p> <p>20 BY MR. SLATER:</p> <p>21 Q. So if I understand correctly in</p> <p>22 publications that you just identified, Number 80 and</p> <p>23 Number 95, you state that there is literature that</p> <p>24 would support an association with certain gastric</p>
<p style="text-align: right;">Page 51</p> <p>1 A. Yes. We divided up different cancer</p> <p>2 types, basically, and assigned them to each other.</p> <p>3 Q. And what exactly is, again -- I just want</p> <p>4 to make sure I understand -- the ASCO -- A-S-C-O --</p> <p>5 self-evaluation program that this was published in?</p> <p>6 What is this?</p> <p>7 A. It's a material source that oncologists</p> <p>8 would use to prepare for their board exams. So it has</p> <p>9 background sections on the cancer, but most of it's</p> <p>10 focused on the treatment guidelines, treatment</p> <p>11 standards, clinical care of patients in various</p> <p>12 settings of the disease. And then there are usually</p> <p>13 question books that come along with it so people can</p> <p>14 prepare for their board exam.</p> <p>15 Q. Did you provide that document or at least</p> <p>16 the chapter that you authored to counsel to produce to</p> <p>17 us?</p> <p>18 A. No, but I'm happy to do so if that's</p> <p>19 required.</p> <p>20 Q. Did you disclose anywhere in that chapter</p> <p>21 that you had been retained by a defendant in this</p> <p>22 litigation where one of the questions was the</p> <p>23 association of certain nitrosamines with certain</p> <p>24 cancers? Was that disclosed in any way there?</p>	<p style="text-align: right;">Page 53</p> <p>1 cancers and there's other literature that is less</p> <p>2 definitive.</p> <p>3 Is that a fair understanding?</p> <p>4 MR. INSOGNA: Object to form.</p> <p>5 A. We were just noting data that's out there</p> <p>6 that's not definitive in a section that's talking about</p> <p>7 risk factors for stomach cancer, to point out that</p> <p>8 studies have been done. And it's not an exhaustive</p> <p>9 reference list either in those reports. There are</p> <p>10 token references that the fellow decided to put in, but</p> <p>11 there are clearly more references that one could</p> <p>12 include on that specific topic.</p> <p>13 BY MR. SLATER:</p> <p>14 Q. From a macro perspective, you would agree</p> <p>15 that there's a potential association between NDMA and</p> <p>16 NDEA and certain cancers? As a general statement, you</p> <p>17 would agree with that; correct?</p> <p>18 MR. INSOGNA: Object to form.</p> <p>19 A. No.</p> <p>20 BY MR. SLATER:</p> <p>21 Q. So you think that anybody who would say</p> <p>22 that there's a potential association between NDMA or</p> <p>23 NDEA and any human cancer would be incorrect?</p> <p>24 MR. INSOGNA: Same objection.</p>

<p style="text-align: right;">Page 54</p> <p>1 A. I think that based on my review, as you 2 can see in my report, I would disagree and I would say 3 that that's an incorrect statement. 4 BY MR. SLATER: 5 Q. So your position is anybody who has any 6 interest in whether or not nitrosamines, including NDMA 7 and NDEA, cause cancer in humans, you would say to them 8 you can stop researching it, you can stop looking at 9 it, there's no potential for these substances to cause 10 cancer in humans? It's a closed book, there's no 11 reason to look at the subject further? 12 MR. INSOGNA: Object to form. Misstates 13 testimony. 14 A. I didn't say that, no. I said that right 15 now if somebody concluded that there is an association, 16 that would be incorrect. I didn't say that further 17 studies should or shouldn't be done. 18 BY MR. SLATER: 19 Q. What if -- well, rephrase. Do you agree 20 that there is a potential association between NDMA and 21 NDEA and certain cancers in humans? 22 MR. INSOGNA: Object to form. 23 A. It is -- they are listed as probable 24 carcinogens in humans by the IARC.</p>	<p style="text-align: right;">Page 56</p> <p>1 risks or benefits of valsartan or similar medications? 2 A. No. 3 Q. Looking now on Page 8 at the heading 4 reviews, which encompasses References 75 to 83. We've 5 talked about Reference 80 just a moment ago. 6 With the exception of Reference 80, do any 7 of these publications address nitrosamines or NDMA or 8 NDEA in any way? 9 A. No. 10 Q. Do any of them address the risks or 11 benefits of valsartan or similar medications? 12 A. No. 13 Q. And just to close the loop on Reference 14 80, other than the specific part that you've told us 15 about, is there any other discussion of nitrosamines? 16 A. No. It's one or two sentences in that 17 section. 18 Q. I think we got through consensus 19 statements and guidelines and book chapters. Looking 20 now at the bottom of Page 9, there's a heading original 21 articles under revision, submitted or in preparation. 22 Do any of those references, which are listed as 1 23 through 5, address nitrosamines in any way? 24 A. No.</p>
<p style="text-align: right;">Page 55</p> <p>1 BY MR. SLATER: 2 Q. And you don't disagree with that; right? 3 A. I don't agree with that statement, no. I 4 don't disagree -- 5 Q. You disagree -- go ahead. I'm sorry. 6 A. No, I wanted to clear up. I don't agree 7 with the IARC statement. 8 Q. I think I skipped over your editorials 9 commentaries heading on Page 8. I think when you told 10 me about your Reference 80, it reminded me that I had 11 skipped a page, so -- 12 Looking at Page 8 of your CV, there's a 13 heading editorials/commentaries? 14 A. Yes. 15 Q. And those are References 65 to 74; 16 correct? 17 A. Yes. 18 Q. Do any of those publications address the 19 issues in this litigation? 20 A. No. 21 Q. Do any of those publications discuss in 22 any way nitrosamines or NDMA or NDEA? 23 A. No. 24 Q. Do any of those publications discuss the</p>	<p style="text-align: right;">Page 57</p> <p>1 Q. Do any of them address the risks or 2 benefits of valsartan or similar medications? 3 A. No. 4 Q. On Page 10, there's a heading that says 5 research support, current grant support. 6 Do any of those listed address the issues 7 in this case? 8 A. No. 9 Q. Specifically, the potential risks of 10 nitrosamines such as NDMA or NDEA? 11 A. No. 12 Q. In the middle of Page 10 there's a heading 13 submitted/planned submission pending grant support. 14 Do any of those items address nitrosamines 15 or the potential risks of nitrosamines? 16 A. No. 17 Q. Do any of them address the risks or 18 benefits of valsartan or similar medications? 19 A. No. 20 Q. And I think I forgot to ask that last 21 question regarding the current grant support. Do any 22 of those items address the risks and benefits of 23 valsartan or similar medications? 24 A. No.</p>

<p style="text-align: right;">Page 58</p> <p>1 Q. Going to the heading on Page 10 that says 2 past grant support, do any of those items address 3 nitrosamines or the potential risks of nitrosamines in 4 any way? 5 A. No. 6 Q. Do any of those address the risks and 7 benefits of valsartan or similar medications? 8 A. No. 9 Q. On Page 11, there's a heading that says 10 oral presentations, invited speaking, international 11 meetings/conferences. Do any of those international 12 meetings or conferences reflect speaking that you've 13 done regarding nitrosamines? 14 A. No. 15 Q. Have you ever spoken, other than in the 16 context of this case, regarding the potential risks of 17 nitrosamines? 18 A. No. 19 Q. Other than in this case, have you ever 20 spoken regarding the question of whether NDMA or NDEA 21 can cause cancer in humans? 22 A. No. 23 Q. Do any of these speaking engagements 24 address the risks and benefits of valsartan or similar</p>	<p style="text-align: right;">Page 60</p> <p>1 Do any of those intramural speaking engagements address 2 nitrosamines or the risks of any nitrosamines? 3 A. No, they do not. 4 Q. Do any of them address the risks and 5 benefits of valsartan or similar medications? 6 A. No, they do not. 7 Q. On the bottom of Page 17, there's a 8 heading that says invited elected service. 9 Do you see that? 10 A. Yes. 11 Q. Do any of those -- I'm going to refer to 12 them as appointments. Do any of them bring with 13 them -- well, rephrase. 14 Looking at the bottom of Page 17 where it 15 says invited elected service, what is that 16 encompassing? 17 A. This is a mix of different things, 18 including intramural positions. Like the first one 19 listed there to be on the clinical trial research 20 committee, which reviews new trials and provides 21 scientific input on how they can be improved before 22 they actually get passed through the IRB, for example. 23 Some of these are -- like the Alliance 24 (ph) one listed there, the third one -- is what's</p>
<p style="text-align: right;">Page 59</p> <p>1 medications? 2 A. No. 3 Q. You said no; correct? 4 A. I said no. Correct. 5 Q. Thank you. Then there's a -- rephrase. 6 Looking at the bottom of Page 12 there's a heading that 7 says national, and I suppose these would be speaking 8 engagements that you've had in the United States? 9 A. Yes. 10 Q. Do any of those speaking engagements 11 address in any way nitrosamines or the risks of 12 nitrosamines? 13 A. No, they do not. 14 Q. Do any of them address the risks and 15 benefits of valsartan or similar medications? 16 A. No, they do not. 17 Q. On Page 15 there's a heading that says 18 regional. Do any of those speaking engagements address 19 nitrosamines in any way? 20 A. No, they do not. 21 Q. Do any of them address the risks and 22 benefits of valsartan or similar medications? 23 A. No, they do not. 24 Q. On Page 16 there's a heading intramural.</p>	<p style="text-align: right;">Page 61</p> <p>1 called a cooperative group of multiple different 2 institutions that are cancer centers that come together 3 to do studies together, and so there are committees in 4 order to get trials through and passed, et cetera, and 5 so I served on that, for example. 6 Some of these are philanthropic groups 7 that I've been asked to serve on the medical advisory 8 committees, you can see there. So it's a mix of -- the 9 ASCO, American Society of Clinical Oncology, set the 10 self-evaluation program that I just -- we were talking 11 about for medical oncologists to get board-recertified. 12 That was an invitation to write that chapter by the 13 society, for example. 14 So that's the flavor of what those types 15 of positions -- and some of them are volunteer work, et 16 cetera -- are. 17 Q. Do any of those positions or the work 18 you've done in connection with those positions address 19 in any way nitrosamines or the risks of nitrosamines? 20 A. No. 21 Q. Do any of them address the risks and 22 benefits of valsartan or similar medications? 23 A. No, they do not. 24 Q. Looking at Page 18, there's a heading</p>

<p style="text-align: right;">Page 62</p> <p>1 editorial activities, and it indicates that you're an 2 ad hoc reviewer for various medical journals; correct? 3 A. Yes. 4 Q. That means a peer reviewer; correct? 5 A. Yes. 6 Q. Have you ever peer-reviewed any article or 7 publication addressing the potential risks of 8 nitrosamines, including NDMA or NDEA, to humans? 9 A. No. 10 Q. Same question regarding potential risks to 11 animals. 12 A. No. 13 Q. On Page 18, there's the heading associate 14 editor, and then another one that says editorial board 15 membership. 16 With regard to those editorial positions, 17 have you ever had occasion to look at or be involved 18 with an article addressing nitrosamines or the 19 potential risks of nitrosamines to humans? 20 A. No. 21 Q. And in those positions have you ever 22 addressed a publication regarding the risks and 23 benefits of valsartan or a similar medication? 24 A. No.</p>	<p style="text-align: right;">Page 64</p> <p>1 journal. And that's after several reviews back and 2 forth with the authors. 3 Q. When a document is finalized through the 4 editorial process that we're discussing, are the 5 references all supposed to be accurate at that point? 6 A. At the end when it goes online or when it 7 gets published, yes. That's what we strive towards. 8 Of course, there are always mistakes to that extent, 9 unfortunately. 10 Q. Even in the peer review process, there can 11 be some mistakes regarding a reference? That can 12 happen; right? 13 A. Absolutely. All -- 14 Q. The fact that someone -- I'm sorry. I 15 didn't mean to interrupt. 16 A. I was going to say, even when I'm 17 publishing myself, I review my manuscript literally 18 hundreds to thousands of times over the course of when 19 it's being written. Inevitably there will be certain 20 spelling errors or things that you only see after the 21 fact after you see it online. 22 The same thing when doing presentations. 23 You present -- you're preparing for a presentation 24 multiple times, and then as you're doing the</p>
<p style="text-align: right;">Page 63</p> <p>1 Q. And with regard to your peer review work 2 and your editorial work, one of the important things is 3 the precision and clarity and accuracy -- rephrase. Let 4 me ask this. 5 With regard to the peer review and 6 editorial work, is it fair to say that the accuracy of 7 what is written in an article that's published in the 8 literature is important? 9 A. Absolutely. 10 Q. In those positions I assume you endeavor 11 to make sure that the references to the statements made 12 within the articles are accurate; correct? 13 A. We do that -- for example, as an associate 14 editor I would be looking at that, but also there are 15 staff that review those types of spelling language 16 because we get a lot of submissions, for example, where 17 English is not the first language, and so there's a lot 18 of editing that's done. 19 The first pass of deciding whether an 20 article has merit is looking at the science and looking 21 at the substance. The other stuff, like spelling, 22 wording, and language, the references, things that are 23 technical like that, are done after the decision is 24 made whether or not this is worth publishing in our</p>	<p style="text-align: right;">Page 65</p> <p>1 presentation sometimes you see, "How did I miss that?" 2 All of those -- I mean, those types of 3 things happen to everybody. We're human. But it 4 doesn't effect the essence of the message that's 5 being -- attempted to be brought forth. 6 Q. So the fact that there may be some errors 7 with some references or spelling or something like that 8 from your perspective doesn't undercut the discussion 9 of the science and the substance, as you phrased it 10 earlier? Do I understand that correctly? 11 MR. INSOGNA: Object to form. 12 A. That's right. 13 THE REPORTER: Sorry. Did you say 14 "right"? 15 A. I said "that's right." 16 THE REPORTER: Thank you. 17 BY MR. SLATER: 18 Q. There's a heading on Page 18 that says 19 clinical protocols. 20 A. Yes. 21 Q. And for the purpose of this question, I'm 22 going to include all the clinical protocols that you've 23 listed in your CV, because there's a whole series of 24 them that follow that heading in different categories;</p>

<p style="text-align: right;">Page 66</p> <p>1 right?</p> <p>2 A. Yes.</p> <p>3 Q. With regard to all of those, do any of</p> <p>4 those clinical protocols address nitrosamines or the</p> <p>5 potential risks of nitrosamines to humans or animals?</p> <p>6 A. No.</p> <p>7 Q. Do any address valsartan, the risks and</p> <p>8 benefits of valsartan or similar medications?</p> <p>9 A. No.</p> <p>10 Q. Going now to Page 23, the next heading is</p> <p>11 teaching activities?</p> <p>12 A. Yes.</p> <p>13 Q. In your teaching, have you ever taught --</p> <p>14 well, rephrase.</p> <p>15 In your teaching, have you ever taught</p> <p>16 specifically with regard to nitrosamines or the risks</p> <p>17 of nitrosamines to humans or animals?</p> <p>18 A. No.</p> <p>19 Q. Have you ever taught regarding valsartan</p> <p>20 or similar medications and their risks and benefits?</p> <p>21 A. Probably did when I was a resident and</p> <p>22 fellow when we're teaching other students. Maybe even</p> <p>23 now when I'm rounding as an inpatient attending with</p> <p>24 medical students, because we take care of patients who</p>	<p style="text-align: right;">Page 68</p> <p>1 have a heading about those research trainees and</p> <p>2 mentees that you've mentored. Has any of that work</p> <p>3 addressed nitrosamines or the risks to humans or</p> <p>4 animals of nitrosamines?</p> <p>5 A. No, it has not.</p> <p>6 Q. Has any of that work addressed the risks</p> <p>7 and benefits of valsartan or similar medications to</p> <p>8 valsartan?</p> <p>9 A. No, it has not.</p> <p>10 Q. And that would be true all the way through</p> <p>11 to the end of your CV on Page 27? That covers that</p> <p>12 whole category; correct?</p> <p>13 A. Yes.</p> <p>14 Q. We can put aside your CV. I think we got</p> <p>15 through it.</p> <p>16 MR. INSOGNA: Adam, are you at an okay</p> <p>17 place to take a break then if you're moving to a new</p> <p>18 document?</p> <p>19 MR. SLATER: Yeah. Let's go off the</p> <p>20 record.</p> <p>21 THE REPORTER: Okay.</p> <p>22 THE VIDEOGRAPHER: We're going off the</p> <p>23 record at 10:45.</p> <p>24 [A brief recess was taken.]</p>
<p style="text-align: right;">Page 67</p> <p>1 are sick who are on these medications, so these types</p> <p>2 of conversations come up in terms of treating patients</p> <p>3 with blood pressure medication, which is very common.</p> <p>4 Q. So an issue could come up -- just because</p> <p>5 a patient might be utilizing that type of medication --</p> <p>6 it could be part of the discussion?</p> <p>7 A. Right, because some of these are -- I</p> <p>8 mean, what I'm listing here are different ways of</p> <p>9 teaching, and one of the predominant ways that I teach</p> <p>10 is through routine patient care with medical students,</p> <p>11 residents, and fellows.</p> <p>12 And so when we're talking about patients</p> <p>13 who are sick, inevitably they're -- many of them are</p> <p>14 taking blood pressure medicine. So I'm sure that these</p> <p>15 types of topics would have come up.</p> <p>16 Q. I'll try to be more precise, then. And I</p> <p>17 understand what you said. With regard to your teaching</p> <p>18 activities, have you ever taught specifically with</p> <p>19 regard to the risks and benefits of valsartan or</p> <p>20 similar medications, other than in the context of maybe</p> <p>21 discussing a particular patient's list of medications</p> <p>22 or what's going on in that patient's background?</p> <p>23 A. Just that. Nothing outside of that.</p> <p>24 Q. And under teaching on Page 24, you then</p>	<p style="text-align: right;">Page 69</p> <p>1 THE VIDEOGRAPHER: We are back on the</p> <p>2 record at 10:59 AM.</p> <p>3 BY MR. SLATER:</p> <p>4 Q. So looking now -- I'm going to skip over</p> <p>5 Exhibit B for a second, and we'll go to Exhibit C of</p> <p>6 your report.</p> <p>7 A. Yes.</p> <p>8 Q. This just lists your fee schedule, and</p> <p>9 those are the fees that you are charging in this</p> <p>10 matter?</p> <p>11 A. Yes.</p> <p>12 Q. So \$750 an hour for your report,</p> <p>13 deposition preparation, for your deposition, for your</p> <p>14 trial preparation, and then \$7,500 a day if you</p> <p>15 actually testify at trial?</p> <p>16 A. Yes.</p> <p>17 Q. Let's look at Exhibit D if we could. And</p> <p>18 for -- and just for the record, we should probably make</p> <p>19 sure that we mark the entire report with all of the</p> <p>20 attachments and exhibits as one exhibit.</p> <p>21 MR. SLATER: I think, Chris, you might</p> <p>22 have marked something else as a separate exhibit. It's</p> <p>23 fine if you did. Like the CV might have been a</p> <p>24 different-numbered exhibit. But let's also have a</p>

<p style="text-align: right;">Page 70</p> <p>1 comprehensive version of the August 27 report with all 2 the attachments and exhibits. That's just for 3 everybody's -- 4 MR. GEDDIS: -- put together as one 5 document, but I can -- 6 MR. SLATER: We'll talk about it -- I want 7 it all as one document. We don't want have to break 8 them up. 9 MR. INSOGNA: And which number would that 10 be, just so that I have it? 11 MR. SLATER: Well, we've already marked 12 the report as Exhibit 7, so that should be the report 13 with all the attachments and exhibits. I think, Chris, 14 you might have marked Exhibit 8 as the CV separately 15 also? 16 MR. GEDDIS: 8 is the CV, then 9 was the 17 Exhibit C, and then Exhibit D I marked as 10. 18 MR. SLATER: Okay. It's fine. There's no 19 harm in doing that. Okay. 20 [Exhibit 8 marked for identification.] 21 [Exhibit 9 marked for identification.] 22 [Exhibit 10 marked for identification.] 23 BY MR. SLATER: 24 Q. Looking now at Exhibit D, Doctor. This is</p>	<p style="text-align: right;">Page 72</p> <p>1 expert or an expert for the defendant, the manufacturer 2 of the asbestos? 3 A. The plaintiff. 4 Q. So you've offered the opinion in that case 5 that that plaintiff's colorectal cancer was caused by 6 asbestos? 7 A. Contributed -- asbestos contributed to 8 cause, yes. 9 Q. Do you have the deposition transcript that 10 you -- from the deposition you gave in October of 2019? 11 A. Yes, we can get it, I think. 12 Q. Do you have the other deposition 13 transcripts for the other depositions listed? 14 A. I don't have them here, but I could get 15 them if necessary. 16 Q. In the deposition in the Gross versus BNSF 17 case, did you offer any opinions about alternative 18 potential causes of the person's colorectal cancer? 19 A. Yes. 20 Q. Did the subject of nitrosamines come up at 21 all in that case? 22 A. No. Not that I recall. 23 Q. In the cases you -- rephrase. You 24 testified the balance of the cases listed here under</p>
<p style="text-align: right;">Page 71</p> <p>1 a listing of your primary testimony, and it should be 2 your prior testimony last four years. 3 Did you compile this list? 4 A. Yes. 5 Q. And you confirmed that this was an 6 accurate list, all-encompassing? 7 A. Yes. 8 Q. Do any of these cases listed here -- well, 9 let me ask you this in general. Are these cases all 10 cases in which you testified as an expert in a medical 11 malpractice case? 12 A. All except for one, I think. 13 Q. Which is the one exception? 14 A. The Deposition Number 7, Gross verse BNSF. 15 Q. Number 7, you said; correct? 16 A. On my list here, yes. 17 Q. What was the subject matter of that case, 18 the Gross versus BNSF case? 19 A. This was -- or it's an ongoing case of a 20 patient with colorectal cancer and exposure to asbestos 21 and causation. 22 Q. And are you the expert for the lawyer -- 23 rephrase. Are you the expert for the plaintiff, 24 meaning the person with the cancer, or are you the</p>	<p style="text-align: right;">Page 73</p> <p>1 trial and deposition are medical malpractice cases; 2 correct? 3 A. I think all the other ones are that. 4 Q. In those cases, are you an expert for the 5 plaintiff, for the defense, or is there a mix? 6 A. There's a mix. 7 Q. Is there any sort of a balance one way or 8 the other where you'd say most of them are for one side 9 or the other? I'm just trying to save walking through 10 them all. 11 A. Yeah, usually when I'm asked that, in 12 general it's about two-thirds to 70 percent plaintiff, 13 and the remainder defendant. 14 Q. To your knowledge, has there ever been a 15 ruling by any court as to the -- your qualifications or 16 whether you could provide any sort of testimony that 17 found either you weren't qualified or you couldn't 18 provide testimony -- anything like that? 19 A. No. 20 Q. How would you define your profession in 21 terms of what you do? What would you describe yourself 22 as? 23 A. I am a medical oncologist that works at an 24 academic center. I subspecialize in GI cancers and I</p>

<p style="text-align: right;">Page 74</p> <p>1 direct the GI oncology program at the University of 2 Chicago, and involved in my roles there, which are 3 multiple different aspects, includes patient care, 4 clinical care of patients that have GI cancers for the 5 most part, but occasionally all cancers, because I do 6 inpatient rounds on sick patients that get admitted 7 with various cancers. 8 I do research -- clinical trial research, 9 laboratory research, something called translational 10 research, which translates findings in the laboratory 11 to clinical research and vice versa, findings from the 12 clinical care of patients back to laboratory questions. 13 I teach along the way on various aspects 14 on clinical care to, as we talked about earlier, 15 medical students, residents, fellows, and also teaching 16 from a research perspective in terms of volunteers and 17 students that come through my research lab and clinical 18 trial research endeavors. 19 I oversee as the GI oncology program -- 20 that's in my report there -- the clinical and the 21 clinical research program for GI cancers at the 22 university, which entails a number of GI medical 23 oncologists -- like we talked about Blase Polite, who 24 is one of them -- and there are others, six at the</p>	<p style="text-align: right;">Page 76</p> <p>1 sense was that your focus of your professional work is 2 on the treatment of cancer but with a specialization 3 and focus on gastrointestinal cancers and trying to 4 develop better ways to treat cancer. 5 Is that a fair understanding in terms of 6 what your main focus is? 7 A. That -- 8 MR. INSOGNA: Object to form. You can 9 answer. 10 A. That's the primary intent of my research 11 agenda, is in the treatment of patients with various GI 12 cancers, yes. 13 BY MR. SLATER: 14 Q. Do you consider yourself to be a 15 toxicologist? 16 A. I do not. 17 Q. Do you consider yourself to be an expert 18 in toxicology? 19 A. I do not. 20 Q. Do you consider yourself to be an 21 epidemiologist? 22 A. I do not. 23 Q. Do you hold yourself out as an expert in 24 epidemiology?</p>
<p style="text-align: right;">Page 75</p> <p>1 moment -- as well as research nurses, clinical nurses, 2 clinical research staff, and overseeing that operation. 3 Also in the umbrella is we have satellite 4 sites at the University of Chicago that are in various 5 places in the Chicagoland area that are part of us and 6 that see patients at those sites, but I oversee the 7 clinical research at those programs as well, and even 8 patients come back and forth from those centers to ours 9 for opinions, et cetera. 10 In addition to that and part of all of 11 that is writing grants to support clinical research 12 questions. We talked about in my CV writing 13 publications, writing commentaries, and in addition to 14 that, other extramural things like we talked about and 15 serving as an editor of journals, reviewing journals to 16 provide back to the scientific community that's not 17 actually -- for example, all those ad hoc reviews 18 aren't paid for per se. They're just -- part of our 19 scientific community is to peer review each other's 20 work. 21 So in a nutshell is all of those things 22 that I do as part of my academic position at the 23 University of Chicago. 24 Q. In reading through your background, my</p>	<p style="text-align: right;">Page 77</p> <p>1 MR. INSOGNA: Form. 2 A. I do not. 3 BY MR. SLATER: 4 Q. Am I correct that you do not consider 5 yourself to be or hold yourself out as an expert in 6 organic chemistry? 7 A. I do not. 8 Q. Do you consider yourself to be an expert 9 in the field of risk assessment? 10 MR. INSOGNA: Object to form. 11 A. I guess it depends on -- can you clarify 12 in maybe a more detailed question? 13 BY MR. SLATER: 14 Q. Risk assessment in the context of somebody 15 who would evaluate whether or to what extent a certain 16 exposure to a certain either chemical or other type of 17 environmental exposure would cause a disease -- for 18 example, cancer -- based on certain levels of exposure 19 for certain durations. 20 Is that something that you do? 21 A. I do not. 22 Q. So you don't consider yourself to be an 23 expert in that field; correct? 24 MR. INSOGNA: Form.</p>

<p style="text-align: right;">Page 78</p> <p>1 A. Correct.</p> <p>2 BY MR. SLATER:</p> <p>3 Q. And I didn't see any such calculations or</p> <p>4 analysis, but did you perform any risk assessment</p> <p>5 calculations along the lines of what I just described</p> <p>6 to you in this case, in your work as an expert in this</p> <p>7 case?</p> <p>8 MR. INSOGNA: Object to form.</p> <p>9 A. Other than what's written in my report in</p> <p>10 terms of the -- for the most part rebutting some of the</p> <p>11 articles that were brought up by expert plaintiffs in</p> <p>12 terms of pointing out certain aspects that I thought</p> <p>13 were flawed or the limitations of the studies, and --</p> <p>14 other than that, I didn't do any other things outside</p> <p>15 of this report.</p> <p>16 BY MR. SLATER:</p> <p>17 Q. And what I'm getting at is, did you</p> <p>18 independently do a risk assessment analysis where you</p> <p>19 calculated doses and duration of use of the valsartan</p> <p>20 pills at issue and do a calculation of what the risk</p> <p>21 level would have been to the various people who might</p> <p>22 have taken the pills?</p> <p>23 MR. INSOGNA: Object to form.</p> <p>24 A. I did a qualitative assessment of the</p>	<p style="text-align: right;">Page 80</p> <p>1 understand. I have your report, and I don't see</p> <p>2 any reference to you doing any independent risk</p> <p>3 assessment or calculations, so I just want to make sure</p> <p>4 I didn't miss that, that there's nowhere where you</p> <p>5 actually say you did a risk assessment or did a</p> <p>6 calculation or came up with the numbers as opposed to</p> <p>7 just commenting on the numbers provided by others?</p> <p>8 A. Right --</p> <p>9 MR. INSOGNA: Object to form. Vague,</p> <p>10 compound.</p> <p>11 A. I was commenting on certain calculations</p> <p>12 and providing my own calculations. Sometimes they</p> <p>13 required calculations.</p> <p>14 BY MR. SLATER:</p> <p>15 Q. With regard to this area, this risk</p> <p>16 assessment toxicology area we're talking about, what</p> <p>17 did you do to ensure that you had seen each of the</p> <p>18 important sources of information? Because you said you</p> <p>19 looked at various literature. What did you do to make</p> <p>20 sure that you had seen everything that was significant?</p> <p>21 A. I reviewed all of the plaintiff expert</p> <p>22 reports which they were relying on for the opinion, and</p> <p>23 from there I did my independent review of the topic</p> <p>24 and -- which includes a lot of the things that I</p>
<p style="text-align: right;">Page 79</p> <p>1 topic, and after reviewing all of the expert --</p> <p>2 plaintiff expert reports and the literature on my</p> <p>3 review, and I provided my opinion based on that review.</p> <p>4 But I didn't do -- because it was my</p> <p>5 understanding that there was a toxicologist who would</p> <p>6 be performing more detailed -- a response to that</p> <p>7 question -- and so I touched on, as I mentioned</p> <p>8 earlier, some of the papers and opinions in terms of</p> <p>9 pointing out limitations, because ultimately I'm not a</p> <p>10 toxicologist or an epidemiologist, as you've pointed</p> <p>11 out. I am a scientist and I can read scientific</p> <p>12 literature and I can provide an opinion based on the</p> <p>13 data that I reviewed.</p> <p>14 BY MR. SLATER:</p> <p>15 Q. Did you do anything to independently</p> <p>16 either verify the calculations or the models or the</p> <p>17 conclusions found in those reports that you were</p> <p>18 commenting on?</p> <p>19 A. I didn't -- sorry.</p> <p>20 MR. INSOGNA: Object to form. Sorry.</p> <p>21 A. I didn't independently do calculations</p> <p>22 outside of what I've already shown in my own report.</p> <p>23 BY MR. SLATER:</p> <p>24 Q. Well, that's what I'm trying to</p>	<p style="text-align: right;">Page 81</p> <p>1 included in my report -- and ultimately I was not</p> <p>2 performing a comprehensive detailed analysis of each of</p> <p>3 those questions.</p> <p>4 I was -- and I think I pointed out in my</p> <p>5 report that I felt compelled to point out the ones that</p> <p>6 were brought forth by plaintiff experts because that's</p> <p>7 what they were relying on -- point out their</p> <p>8 limitations.</p> <p>9 Q. So if I understand correctly, in terms of</p> <p>10 what the plaintiffs' experts opinions were, you saw</p> <p>11 yourself as providing basically rebuttal to what they</p> <p>12 said, as opposed to providing your own independent</p> <p>13 analysis from scratch?</p> <p>14 Do I understand that correctly?</p> <p>15 MR. INSOGNA: Object to form. Misstates</p> <p>16 testimony.</p> <p>17 A. Because I'm not an epidemiologist or a</p> <p>18 toxicologist and my understanding was that there would</p> <p>19 be experts providing a more detailed and comprehensive</p> <p>20 response, I focused on pertinent to these particular</p> <p>21 topics as I mentioned earlier, the reports and the</p> <p>22 papers and the opinions that were brought forth by the</p> <p>23 plaintiff experts, presuming that all of the ones</p> <p>24 that -- all of the topics and papers that they were</p>

<p style="text-align: right;">Page 82</p> <p>1 using in favor of their arguments would be 2 comprehensive. They wouldn't exclude ones that they 3 thought were important to their opinion. So I focused 4 on the ones that they brought forth. 5 And this is because -- I think I should 6 sort of establish this -- is that whenever we have a 7 scientific question and you have a proposed hypothesis, 8 the null hypothesis is that it's negative, that 9 there's, say in this case, no association, and that you 10 have to show evidence to reject that null hypothesis 11 and to accept the alternative. 12 And so if I'm reviewing it from the 13 perspective that I'm looking at the data that have been 14 provided to me to try and reject the null hypothesis 15 and accept the alternative, I was looking at the data 16 that was being brought forth to make that assessment, 17 and those articles are the ones that are in the 18 plaintiff experts' reports, so I focused on those to 19 address those to see if I agreed or not with that 20 opinion. 21 BY MR. SLATER: 22 Q. So if I understand correctly, you didn't 23 independently research these issues; you looked at what 24 the plaintiff experts had referred to, and those</p>	<p style="text-align: right;">Page 84</p> <p>1 MR. INSOGNA: Object to form. 2 A. No, I followed what I normally would do, 3 which is start with a question, and whatever data I 4 have to start with it, and then perform a more 5 extensive literature search on the topic. 6 BY MR. SLATER: 7 Q. Is it your testimony that you reviewed in 8 its entirety every single report written by the 9 plaintiff experts and every single piece of literature 10 that was referenced by all the plaintiff experts? 11 MR. INSOGNA: Object to form. 12 A. Only the ones that are in my reliance list 13 are the ones that I relied on to make my opinion. So 14 the answer is no, I didn't look at every -- look at 15 every reference in great detail from the expert 16 plaintiffs. But I looked at what I thought were 17 their -- the articles that they were putting most of 18 the emphasis of their opinions on, that they relied on 19 heavily. 20 BY MR. SLATER: 21 Q. Part of your methodology is to review 22 those source materials which were most significant? 23 That was what you endeavored to do; correct? Let me 24 ask it differently.</p>
<p style="text-align: right;">Page 83</p> <p>1 materials were provided to you by counsel, and that's 2 what you reviewed; correct? 3 MR. INSOGNA: Object to form. 4 A. That's where I started, with those 5 articles, and I did an independent review, and there 6 are articles in my report, for example, that they do 7 not reference. I looked outside of their reports, but 8 it was all focused on that question based on the 9 original articles that the plaintiff experts used 10 with -- 11 BY MR. SLATER: 12 Q. You mentioned -- I'm sorry. Go ahead. 13 A. I was going to say, we're talking about 14 the toxicology and the epidemiology question. 15 Q. Right. In terms of the level of rigor 16 that you follow in your methodology when you, for 17 example, publish something yourself or review it -- 18 review something else somebody else wants to publish -- 19 let me rephrase. 20 With regard to the epidemiology and 21 toxicology opinions, from what I'm hearing, you didn't 22 follow the same sort of process you would have followed 23 if you were actually authoring original research or an 24 original paper; correct?</p>	<p style="text-align: right;">Page 85</p> <p>1 In terms of your method -- in terms of 2 a -- rephrase. In terms of a scientific methodology, 3 you were reviewing various materials -- literature, for 4 example -- you wanted to make sure that you saw that 5 literature which was most significant with regard to 6 the questions you were trying to answer; right? 7 A. Yes. 8 Q. And if it turns out that you didn't review 9 or consider something that was significant, that could 10 potentially undercut the ultimate opinion; correct? 11 MR. INSOGNA: Object to form. 12 A. If there was an article that was pivotal 13 or instrumental for the opinion to reject the null 14 hypothesis, and accept the alternative hypothesis and I 15 didn't see that, then that would be -- that would not 16 be good. 17 BY MR. SLATER: 18 Q. In your report was it important for you to 19 accurately characterize the findings in the studies 20 that you discussed? 21 A. Yes, that would be an important thing to 22 do -- strive to do. 23 Q. For example, in your peer review or 24 editorial work, if you were to find or be told that</p>

<p style="text-align: right;">Page 86</p> <p>1 somebody said something in a proposed article that 2 mischaracterized a source of information, that would be 3 a problem and that would have to be fixed or the 4 article would have to be withdrawn; right? 5 MR. INSOGNA: Object to form. 6 BY MR. SLATER: 7 Q. If it was something of significance? 8 A. There's -- if something found after the 9 fact that's of significance, then articles can be 10 edited or amended or retracted. 11 Q. Did you think that it was important for 12 you to independent verify that each of the statements 13 you made characterizing the findings in the articles 14 you discussed were accurate? 15 A. Yes. That was what I would strive to do 16 when I wrote my report -- ensure that things are 17 accurate. 18 Q. You talked earlier about your work 19 regarding research and actually being involved in the 20 process to vet proposed research; correct? 21 A. Yes. 22 Q. We talked about that a little earlier? 23 A. Yes. 24 Q. And my understanding is none of the</p>	<p style="text-align: right;">Page 88</p> <p>1 and the reading you've done, you would agree with me 2 that there's no IRB in the country that would agree to 3 let that study go forward, because it would be 4 unethical; right? 5 A. I don't know the details of the study that 6 you're proposing, so I can't comment. 7 Q. All right, here's the study. We're going 8 to get the valsartan pills that were manufactured by 9 ZHP with the levels of NDMA that you've commented on in 10 your report and we're going to give those pills to 11 humans for five years every day, and we're going to 12 have another set of people that's going to take 13 valsartan that we know has no contamination risk at 14 all, and we're going to see how those people do over 15 the next 30 years. 16 Is that an ethical study? 17 MR. INSOGNA: Object to form. 18 A. Are they randomized? 19 BY MR. SLATER: 20 Q. Either way, whether they're randomized or 21 not, people are going to get those pills that ZHP 22 produced and they're going to take them for five years 23 with those contamination levels of NDMA. 24 Is that an ethical study that could be</p>
<p style="text-align: right;">Page 87</p> <p>1 research that you've either personally participated in 2 or had a responsibility to review at some level has -- 3 none of that has addressed nitrosamines or the 4 potential risks to humans of nitrosamines; right? 5 A. Right. 6 Q. For example, there's no study that you've 7 either been involved in or had presented to you as a 8 proposed study where NDMA would be given to human 9 beings to see what the effect would be on the human 10 beings? 11 Has there ever been any such study like 12 that you've been involved in? 13 A. No. 14 Q. If somebody walked into your office 15 tomorrow morning and said, "I want to do a study where 16 I'm going to give NDMA to humans and we're going to 17 have a control group that's not going to get NDMA," do 18 you think that has a chance to pass muster with the 19 IRB? 20 A. I wouldn't be involved in such a study in 21 my capacity in what I do from a research perspective 22 because I'm more involved in treating cancer, so that 23 wouldn't happen. 24 Q. Well, based on what you know about NDMA</p>	<p style="text-align: right;">Page 89</p> <p>1 approved? 2 A. I don't know. 3 Q. In all of the research you've done, in all 4 the reading you've done since you were first contacted 5 in this case back in March of this year, have you seen 6 any study where human beings were deliberately given 7 NDMA at the levels found -- and I'll use, for example, 8 at the levels found in the ZHP-manufactured valsartan. 9 Have you seen any study where that was 10 deliberately done? 11 A. I have not seen any studies where NDMA was 12 given deliberately in a randomized fashion, but I've 13 seen one prospective randomized study that gave 14 ranitidine, which putatively degrades or is activated 15 to have NDMA endogenously after taking it to patients 16 or not and following certain parameters. I think the 17 primary end point was excretion of NDMA in the urine 18 and changes with and without. 19 That would be the closest thing that would 20 be a prospective study that evaluated that -- something 21 like known exposures to something that putatively 22 causes something, to address the question in a 23 scientific manner. 24 Q. It was your understanding that the</p>

<p style="text-align: right;">Page 90</p> <p>1 ranitidine study was conducted with the intent of 2 exposing people to NDMA to see what it would -- how it 3 would affect them? 4 MR. INSOGNA: Objection. 5 A. It's been a while since I read that paper, 6 but it was intended to evaluate levels of excretion of 7 NDMA and changes with or without ranitidine. 8 BY MR. SLATER: 9 Q. Is that the study that had to be withdrawn 10 from the literature? 11 A. Not that I'm aware of. It was published 12 in JAMA here. And that obviously wasn't determined to 13 be unethical, because it was conducted and published. 14 Q. Where was that study done? 15 A. I don't know. I'd have to look up the 16 paper again. 17 Q. Is the paper listed in your report? 18 A. No. You asked me if I knew of a study 19 that did something like that, so that's why I'm telling 20 you. 21 Q. No, that's fine. That was what I asked 22 you. It was a new question. 23 Let's go now to Exhibit B to your report. 24 A. Okay.</p>	<p style="text-align: right;">Page 92</p> <p>1 file transfer this week, or are you asking about the 2 August 27th? 3 MR. SLATER: I'm asking about the August 4 27th, but it could apply to either because I'm just 5 asking about the purpose of the list. So the purpose 6 would be the same, I would assume, regardless of which 7 version it is. But let me ask the question again. 8 BY MR. SLATER: 9 Q. This amended list of materials considered 10 which is attached as Exhibit B to your August 27 11 report -- what is that supposed to convey? What is 12 that document? 13 A. This lists all of the documents that I 14 reviewed that were pertinent for me to either include 15 in my report or had some contribution to formulating my 16 opinion. 17 Q. The exhibit we just marked as Exhibit 11 18 was provided to us when your files were provided to us. 19 To your knowledge, was that an updated 20 version of this amended list of materials considered? 21 A. I think so. 22 Q. Do you know what was edited and why in the 23 most recent version, which is Exhibit 11? 24 A. I don't know offhand.</p>
<p style="text-align: right;">Page 91</p> <p>1 Q. Exhibit B to your report of August 27, 2 2021, is titled amended list of materials considered. 3 Do you see that? 4 A. Yes. 5 MR. SLATER: And Chris, let's mark as an 6 exhibit separately the updated amended list of 7 materials that we were provided with the production. 8 Let's mark that as Exhibit -- I don't know what number 9 we're up to. Are we now up to Exhibit 11 or 12? 10 MR. GEDDIS: 11. It's 11. 11 THE REPORTER: So this is going to be 12, 12 Chris? 13 MR. GEDDIS: No, this is going to be 14 Exhibit 11. 15 THE REPORTER: Okay. Very good. 16 [Exhibit 11 marked for identification.] 17 BY MR. SLATER: 18 Q. Doctor, what I'm trying to understand -- 19 well, rephrase. Looking now at the Exhibit B to your 20 August 27 report, is this intended to be comprehensive 21 of everything you reviewed as part of your analysis of 22 the questions that you answered in your report? 23 MR. INSOGNA: Object to form. Adam, are 24 you asking about the update that came through in the</p>	<p style="text-align: right;">Page 93</p> <p>1 Q. Was there anything that you had located or 2 identified as having not been included that should be 3 so that you said, "I need to make sure this gets 4 included"? 5 A. There may have been a paper, but maybe -- 6 forget the name of the author -- but there was one 7 paper about nonlinear estimations of dosing. Patrick I 8 think is the name of the author. 9 Q. Who? 10 A. I think it's -- I could be wrong. I can 11 get the name if you give me a second. It's Gerald. 12 Excuse me. 13 Q. Looking now -- well, let me ask you this. 14 Do you have Exhibit 11, the most updated amended list 15 of materials, available to you? 16 A. I have a lot of them and we're trying to 17 determine which one's the most recent one. This is the 18 most recent one. So yes. 19 Q. Okay, great. I'm going to use that as the 20 exhibit we're going to talk about now, because it's the 21 most up-to-date amended list of materials we were 22 provided before the deposition. Okay? 23 A. Okay. 24 Q. Looking at the first category, MDL</p>

<p style="text-align: right;">Page 94</p> <p>1 pleadings and general documents, did you rely on any of 2 those documents in forming your opinions in this case? 3 MR. INSOGNA: Object to form. Vague. 4 A. No, not really. 5 BY MR. SLATER: 6 Q. Did you read each of those documents? 7 A. Yes. I've looked through all of these 8 documents, as I mentioned at the very beginning, some 9 in more detail than others, though, that I put more 10 emphasis on than others. 11 Q. When you say you looked through a 12 document, I take that to mean that you may have skimmed 13 it or jumped around to get a gist of a document as 14 opposed to reading an entire document. 15 Do you make the same distinction when you 16 say you looked at a document versus read the entire 17 document? 18 A. Yes, sometimes I would skim through it, 19 and other times I would really focus and sometimes read 20 it five times, like a specific article, for example. 21 Q. So if I understand the MDL pleadings in 22 general documents category, you looked through those 23 documents but didn't rely on anything in those 24 documents to form your opinions; is that correct?</p>	<p style="text-align: right;">Page 96</p> <p>1 A. It served as the basis of the starting 2 point of what was happening. 3 Q. Anything else that you relied on in those 4 documents to form your opinions? 5 MR. INSOGNA: Object to form. 6 A. I would have to go back and look to see 7 exactly what's in them again, but -- I can think of at 8 the moment. 9 BY MR. SLATER: 10 Q. There's a list of expert reports with 11 exhibits. Did you read each of those expert reports 12 cover to cover? 13 A. Yes. 14 Q. Did you rely on those expert reports or 15 any parts of them in forming your own opinions? 16 MR. INSOGNA: Object to form. Vague. 17 A. As we talked about earlier, I used those 18 reports as a starting point of what the argument was in 19 terms of the opinion to reject the null hypothesis and 20 accept the alternative hypothesis. So those were the 21 reports that -- where the substance of that opinion 22 lied. 23 BY MR. SLATER: 24 Q. Did you see anything in those reports that</p>
<p style="text-align: right;">Page 95</p> <p>1 MR. INSOGNA: Object to form. Vague. 2 Mischaracterizes. 3 A. I think some of those would have had the 4 original cancer types listed, for example, that are 5 part of the litigation, so of course I focused on those 6 because that's what I was trying to focus on in my 7 report. 8 BY MR. SLATER: 9 Q. So your answer is, with regard to that 10 category of documents, the listing of cancers that were 11 at issue was informative to you of what you were going 12 to be addressing in your report? Do I understand that? 13 A. As an example -- 14 MR. INSOGNA: Objection. 15 A. As an example to what I used those initial 16 documents for. 17 BY MR. SLATER: 18 Q. Is there anything else that you used those 19 initial documents for, the MDL pleadings and general 20 documents -- that list right there? 21 A. Get an understanding of what the whole 22 question was at hand. 23 Q. Did you rely on that in forming your 24 opinions?</p>	<p style="text-align: right;">Page 97</p> <p>1 you found to be accurate with regard to the question 2 that you were looking at, meaning did you look at any 3 of the expert reports from the plaintiff experts and 4 say, "I agree with that. That's a good point"? 5 MR. INSOGNA: Object to form. Vague, 6 compound. 7 A. If the question is, was the report 100 8 percent inaccurate, then the answer to that is no -- 9 every topic and every opinion stated there. 10 BY MR. SLATER: 11 Q. Do you agree with me it was important for 12 you in writing your report to focus both on those 13 things that were supportive of the position that you 14 were taking, as opposed -- as well as that information 15 which was contrary to the position that you were 16 taking? 17 A. That's how science works, yes. You have 18 to look at all the data on a pertinent question and 19 make an assessment if there is enough information there 20 that would lead you to reject null hypothesis and 21 accept the alternative hypothesis. 22 Q. So for example, if there was an article 23 that you found to be important in forming your 24 opinions, was it also important for you in your report</p>

<p style="text-align: right;">Page 98</p> <p>1 to talk about those aspects of that article that</p> <p>2 supported your opinion as well as those parts of the</p> <p>3 article that would cut against your opinion and be</p> <p>4 supportive of the plaintiff position?</p> <p>5 Did you feel it was important to address</p> <p>6 both sides of that coin in your report?</p> <p>7 MR. INSOGNA: Object to form.</p> <p>8 A. Yes, which I strive to do, is to show all</p> <p>9 the evidence, the discussion points around them, and an</p> <p>10 overall opinion as to where my -- where the data lie in</p> <p>11 terms of whether or not it's enough to sway away from</p> <p>12 the null hypothesis or not.</p> <p>13 So it's not often that you would see all</p> <p>14 data point to one thing. The way science works is that</p> <p>15 there are different outcomes with different studies,</p> <p>16 and ultimately you have to look at the data as a whole</p> <p>17 in terms of whether or not there's consistency with the</p> <p>18 findings, what type of evidence we're talking about,</p> <p>19 because I think as we'll get to along the way here,</p> <p>20 different studies are different and contribute</p> <p>21 different things to the understanding of the question</p> <p>22 at hand and have different emphasis and weight in terms</p> <p>23 of ultimately how you're going to make your final</p> <p>24 opinion.</p>	<p style="text-align: right;">Page 100</p> <p>1 of the data or the findings that were supportive of</p> <p>2 your position that you also make sure you pointed out</p> <p>3 the data and findings that was not supportive of your</p> <p>4 position if there was such information?</p> <p>5 MR. INSOGNA: Object to form.</p> <p>6 A. I think I answered that in the sense that</p> <p>7 all the data that was not ultimately in line with my</p> <p>8 opinion is referenced there, because that was where I</p> <p>9 started, was where the plaintiff experts were using</p> <p>10 that.</p> <p>11 And I think it should be stated that the</p> <p>12 way science works is that you don't have to disprove</p> <p>13 the null hypothesis; you have to prove the alternative</p> <p>14 hypothesis in order to reject the null hypothesis. The</p> <p>15 onus is not on me to prove that it's not true. I'm</p> <p>16 looking at the data that's being provided to me to try</p> <p>17 and sway me away from that.</p> <p>18 BY MR. SLATER:</p> <p>19 Q. My question is not -- well, again --</p> <p>20 rephrase. Again, what I'm -- rephrase. What I'm</p> <p>21 asking you is, when you wrote your report and discussed</p> <p>22 a particular study, in terms of a valid methodology of</p> <p>23 writing this type of a report, you needed to reflect in</p> <p>24 your report the information that was supportive of your</p>
<p style="text-align: right;">Page 99</p> <p>1 So yes, though, you have to look at all</p> <p>2 available data that's there and then, taking all those</p> <p>3 points into account, come up with a decision whether or</p> <p>4 not you think there's enough to be swayed away from the</p> <p>5 null hypothesis. That's how science works. You don't</p> <p>6 ignore data.</p> <p>7 BY MR. SLATER:</p> <p>8 Q. Not only were you obligated to look at all</p> <p>9 of the data and look at the data on both sides of the</p> <p>10 question, but you would agree with me you also in your</p> <p>11 report, if you were going to cite an article, needed to</p> <p>12 talk about the information that was both pro and con to</p> <p>13 the position you were taking in order to be evenhanded;</p> <p>14 correct?</p> <p>15 MR. INSOGNA: Object to form.</p> <p>16 Argumentative.</p> <p>17 A. Which is why I've referenced all of the</p> <p>18 articles that the expert plaintiffs rely on for their</p> <p>19 opinion.</p> <p>20 BY MR. SLATER:</p> <p>21 Q. It's a little bit of a different question.</p> <p>22 In writing your report where you evaluated the</p> <p>23 literature and the studies, was it important for you to</p> <p>24 make sure that if you were going to point out aspects</p>	<p style="text-align: right;">Page 101</p> <p>1 position but also to be evenhanded to discuss in your</p> <p>2 report the data that wasn't?</p> <p>3 I'm not saying just citing the article,</p> <p>4 but actually discussing with substance, "They say this.</p> <p>5 That was important to me. It supports this. They also</p> <p>6 say this, though, and I do have to acknowledge that</p> <p>7 could go the other way."</p> <p>8 Should you have been evenhanded like that?</p> <p>9 MR. INSOGNA: Object to form.</p> <p>10 Argumentative.</p> <p>11 A. And the answer to that is yes, and I mean,</p> <p>12 I can go through and find examples, but as an example</p> <p>13 that comes to mind, I pointed out limitations of</p> <p>14 articles that I was relying on that ultimately don't</p> <p>15 show an association but that there were limitations to</p> <p>16 the study, like there are -- in all studies there are</p> <p>17 some limitation. So that's an example of showing both</p> <p>18 sides, and from a scientific perspective that's normal</p> <p>19 and natural to do something like that.</p> <p>20 BY MR. SLATER:</p> <p>21 Q. From a scientific perspective, it would</p> <p>22 never be acceptable to mischaracterize the data in a</p> <p>23 study and describe it in such a way that it spins the</p> <p>24 article and the findings one way or the other; right?</p>

<p style="text-align: right;">Page 102</p> <p>1 MR. INSOGNA: Object to form.</p> <p>2 A. Not in an intentional malignant way.</p> <p>3 That's an opinion that one takes out of the data and</p> <p>4 that's their opinion based on how it's interpreted,</p> <p>5 and -- for example, some studies provide data and</p> <p>6 can -- some physicians interpret it differently than</p> <p>7 others, and it's different interpretation of the data.</p> <p>8 BY MR. SLATER:</p> <p>9 Q. It certainly would never be acceptable to</p> <p>10 characterize the data and findings in the study in such</p> <p>11 a way that doesn't accurately reflect what the article</p> <p>12 actually says; right?</p> <p>13 MR. INSOGNA: Same objection.</p> <p>14 A. Sometimes, for example, I don't agree with</p> <p>15 every point or conclusion that is mentioned in an</p> <p>16 article, so for me to opine on that I think is part of</p> <p>17 the scientific method.</p> <p>18 Sometimes statements in articles are</p> <p>19 speculative or trying to explain a phenomenon, but that</p> <p>20 doesn't make the statement in an article a gold</p> <p>21 standard, and that's just the author's interpretation</p> <p>22 or thoughts, but it doesn't make it the -- it's not</p> <p>23 infallible, if that's the question. So I can review</p> <p>24 the same dataset and provide my own opinions on that</p>	<p style="text-align: right;">Page 104</p> <p>1 bit vague what we're talking about here. Like are</p> <p>2 these two data points? Is one a primary end point and</p> <p>3 others are secondary end points? Because that is an</p> <p>4 important thing to consider.</p> <p>5 But I'm not sure what you're asking, but</p> <p>6 of course, if it's a data point, then it should not be</p> <p>7 mischaracterized or changed -- the number changed, for</p> <p>8 example, intentionally.</p> <p>9 BY MR. SLATER:</p> <p>10 Q. We talked a little bit earlier about the</p> <p>11 toxicology and epidemiology aspects of your analysis.</p> <p>12 Remember that?</p> <p>13 A. Yes.</p> <p>14 Q. And I think you told me that you knew that</p> <p>15 there were other people that were actual toxicologists</p> <p>16 and epidemiologists who were going to address that in a</p> <p>17 thorough manner, so you didn't feel like you needed to</p> <p>18 get into that kind of depth because there were other</p> <p>19 people analyzing that.</p> <p>20 Do I understand that correctly?</p> <p>21 MR. INSOGNA: Object to form.</p> <p>22 Mischaracterizes the testimony.</p> <p>23 A. I was informed that there would be</p> <p>24 specific experts asking those questions from that</p>
<p style="text-align: right;">Page 103</p> <p>1 data.</p> <p>2 BY MR. SLATER:</p> <p>3 Q. With regard to objective data points, it</p> <p>4 would never be acceptable to mischaracterize those</p> <p>5 objective data points; correct?</p> <p>6 A. No, if there were -- if it was about a</p> <p>7 number or something that was a data point and it was</p> <p>8 misrepresented, that could happen, but that's not what</p> <p>9 I'm talking about. That would be -- that's not how</p> <p>10 science works. You can't change the dataset.</p> <p>11 Q. If there's objectively-reported data in</p> <p>12 the study that you're talking about, it would not be</p> <p>13 scientifically-acceptable to talk in your report about</p> <p>14 that objective data that's supportive of your position</p> <p>15 while not referencing and discussing on the other hand</p> <p>16 other objective data in the study if it actually is</p> <p>17 supportive of the opposite position; right?</p> <p>18 You have to be evenhanded in what you</p> <p>19 discuss in your report; right?</p> <p>20 MR. INSOGNA: Object to form.</p> <p>21 Argumentative, mischaracterizes.</p> <p>22 A. You would strive to do that, and I'm not</p> <p>23 sure what example -- because maybe it's an example that</p> <p>24 we should have the details of, because it's a little</p>	<p style="text-align: right;">Page 105</p> <p>1 perspective, and so -- and I'm not a toxicologist or an</p> <p>2 epidemiologist, but at the same time I think I</p> <p>3 mentioned earlier I can read papers, scientific papers,</p> <p>4 and evaluate their strengths and limitations and</p> <p>5 evaluate them in terms of my ability to formalize an</p> <p>6 opinion on a given question that is a scientific</p> <p>7 question.</p> <p>8 BY MR. SLATER:</p> <p>9 Q. Had you authored -- go ahead. I'm sorry.</p> <p>10 A. I was going to say, the language of</p> <p>11 science is universal in terms of understanding how to</p> <p>12 apply scientific method -- different disciplines of</p> <p>13 science like epidemiology, biology, chemistry,</p> <p>14 epidemiology, toxicology -- but the methods with which</p> <p>15 one tests hypotheses, as we've been alluding to all</p> <p>16 along the way here, is the same. So I can weigh data</p> <p>17 in the same manner.</p> <p>18 Q. In terms of the -- what you just referred</p> <p>19 to as weighing the data, would you agree with me that</p> <p>20 the toxicologists and epidemiologists in this case did</p> <p>21 that in a more rigorous manner than you did because</p> <p>22 that's their specialty?</p> <p>23 MR. INSOGNA: Object to form.</p> <p>24 A. They did it in their manner from the way</p>

<p style="text-align: right;">Page 106</p> <p>1 they do it in their discipline, yes. I looked at it, 2 as I mentioned earlier and in my report, after 3 reviewing the plaintiff experts' reports and seeing the 4 papers that they were relying on for their opinion and 5 evaluating those papers and pointing out limitations 6 and strengths from those papers and how that played a 7 role into my opinion that I was asked to give, which 8 one of them was the question at hand -- is, is there an 9 association with cancer risk with the trace impurities 10 that were found in these agents or not based on the 11 available evidence to date? 12 BY MR. SLATER: 13 Q. You just used the word trace impurities. 14 How do you define that term? 15 A. How do I define it? I -- 16 Q. Yeah. Why did you use the word trace? 17 What does that mean? 18 A. Because they're small -- like they're very 19 small amounts in each of the -- in the pills. I mean, 20 that's what they were referred to in many of the 21 reports and in the FDA reports that I read and 22 referenced. 23 Q. The amounts of NDMA in the various pills 24 varied depending on the manufacturer.</p>	<p style="text-align: right;">Page 108</p> <p>1 MR. INSOGNA: Object to form. Vague. 2 A. I don't have them in front of me, but I 3 know that the answer to that is no. The levels are far 4 lower. 5 BY MR. SLATER: 6 Q. And that's based on, which we're going to 7 get to later, your understanding about how much 8 exogenous or endogenous NDMA one may be exposed in 9 everyday life? 10 A. Right. That's right. 11 Q. On the first page of this list of 12 materials considered, there's a heading deposition 13 transcripts with exhibits. 14 Did you read each of those deposition 15 transcripts in their entirety? 16 A. Yes. Yes. 17 Q. Did you read all the exhibits in their 18 entirety? 19 A. I looked at as many as I could. I didn't 20 read them all in detail, no. I focused more on the 21 deposition itself. Some of the -- what did you call 22 them -- attachments? Is that what they're called -- 23 the attachments? 24 Q. To the report?</p>
<p style="text-align: right;">Page 107</p> <p>1 Are you aware of that? 2 A. Yes. 3 Q. Are you saying that all of those levels 4 right up to the highest level seen are all trace 5 amounts and very small? 6 A. Yes. 7 Q. What's your frame of -- what's your basis 8 for that opinion? 9 A. All in my report in terms of looking at 10 our daily exposures to NDMA based on exogenous and 11 what's endogenous, the estimates of endogenous -- the 12 levels that are found in these pills are minuscule 13 compared to that, so that's what the word trace means 14 to me, is that there are small amounts. 15 Many of the lots there was nothing 16 detected, below the limit of detection, and all the 17 levels are relatively low compared to the known levels 18 that we are exposed to on a daily basis based on the 19 references and studies that I pointed out in my report 20 and after the fact seeing that in many of the other 21 expert reports. 22 Q. Did you see any levels of NDMA in any of 23 the pills that exceeded the levels that one may be 24 exposed to through just background exposure?</p>	<p style="text-align: right;">Page 109</p> <p>1 A. Yeah. 2 Q. Exhibits? 3 A. Exhibits. Excuse me. Many of them are 4 articles that were -- I already read because they were 5 part of the original review of generating my own 6 report, but yes. Did I read through everyone's CV 7 entirely? No. 8 Q. One of the materials listed here is the 9 transcript of Raphael Nudelman deposition. 10 Who is that? 11 A. That is a deposition, as I looked at that 12 name, that I read right near the beginning. You can 13 see the date there. I think it was in April. So I'd 14 have to look at it again to remind and refresh my 15 memory what it was. 16 Q. As you sit here now, you're not sure who 17 Raphael Nudelman is? 18 A. I can't remember -- 19 Q. One of the things you said -- go ahead. 20 I'm sorry. 21 A. I was going to say, I haven't reviewed 22 that deposition recently. 23 Q. One of the things you told me earlier was 24 that these materials were provided to you by defense</p>

<p style="text-align: right;">Page 110</p> <p>1 counsel; correct?</p> <p>2 MR. INSOGNA: Object to form. Misstates</p> <p>3 testimony.</p> <p>4 A. Some of them.</p> <p>5 BY MR. SLATER:</p> <p>6 Q. Well, I guess the transcript will speak</p> <p>7 for itself. With regard to the -- new question. With</p> <p>8 regard to the materials that defense counsel provided</p> <p>9 to you, did you expect that defense counsel would give</p> <p>10 you materials that would not only be supportive of the</p> <p>11 position that you were going to take, but also those</p> <p>12 materials that could cut against the position you were</p> <p>13 going to take?</p> <p>14 MR. INSOGNA: Object to form.</p> <p>15 Mischaracterizes testimony.</p> <p>16 A. In terms of actual literature, I didn't</p> <p>17 expect them to provide me with anything, really. I</p> <p>18 would do my own independent research. In terms of</p> <p>19 depositions and some of these other legal documents,</p> <p>20 then the answer is yes. I would be expecting to</p> <p>21 receive all the pertinent records for balanced decision</p> <p>22 and opinion.</p> <p>23 BY MR. SLATER:</p> <p>24 Q. And that's the key, is that you --</p>	<p style="text-align: right;">Page 112</p> <p>1 MR. INSOGNA: Object to form. Assumes</p> <p>2 facts. Argumentative.</p> <p>3 A. Yes, I would like to see all the documents</p> <p>4 that were known on either side of the opinion.</p> <p>5 BY MR. SLATER:</p> <p>6 Q. For example, if there were internal</p> <p>7 documents from Teva, for example, in which people at</p> <p>8 Teva were recognizing the danger to humans of NDMA and</p> <p>9 NDEA in the Teva valsartan, you would have wanted to</p> <p>10 see that so you could take it into account in your</p> <p>11 analysis; right?</p> <p>12 MR. INSOGNA: Object to form. Assumes</p> <p>13 facts, argumentative.</p> <p>14 A. We're talking about discussions amongst</p> <p>15 employees at the company?</p> <p>16 BY MR. SLATER:</p> <p>17 Q. No, we're talking about -- well, it would</p> <p>18 include that -- let me rephrase. It would include</p> <p>19 that. It could also include an analysis of this</p> <p>20 particular question, like when the company found out</p> <p>21 there was NDMA in its valsartan, their internal</p> <p>22 analysis of the risk to humans.</p> <p>23 You'd want to see that; right?</p> <p>24 MR. INSOGNA: Same objection.</p>
<p style="text-align: right;">Page 111</p> <p>1 ultimately if you're doing something that's</p> <p>2 scientifically appropriate in terms of methodologies,</p> <p>3 to have a balanced dataset; right?</p> <p>4 MR. INSOGNA: Object to form.</p> <p>5 BY MR. SLATER:</p> <p>6 Q. Meaning the data on both sides of the</p> <p>7 question; right?</p> <p>8 MR. INSOGNA: Same objection.</p> <p>9 A. Yeah, I think we've alluded to that</p> <p>10 particular question about data, as opposed to like a</p> <p>11 deposition that happened previously.</p> <p>12 BY MR. SLATER:</p> <p>13 Q. For exam -- rephrase. You relied on</p> <p>14 defense counsel to get you the pertinent legal</p> <p>15 documents -- things like depositions, things like</p> <p>16 internal corporate documents; correct?</p> <p>17 A. Yes.</p> <p>18 Q. And if there were such documents that</p> <p>19 existed that would support the position that you are</p> <p>20 contrary to, the position -- well, rephrase.</p> <p>21 If there were such documents that</p> <p>22 supported the position that NDMA and NDEA can cause</p> <p>23 cancer in humans, you would have wanted to see that;</p> <p>24 right?</p>	<p style="text-align: right;">Page 113</p> <p>1 A. I would like to see all evidence as much</p> <p>2 as possible, yes. The more data -- I wouldn't exclude</p> <p>3 data. Whether it would be important in my decision is</p> <p>4 another question, but if there was evidence or some</p> <p>5 sort of data, then of course, you have to -- what is</p> <p>6 available, you review and assess.</p> <p>7 BY MR. SLATER:</p> <p>8 Q. For example, if there was deposition</p> <p>9 testimony or internal documents from one of the</p> <p>10 manufacturers in which it was acknowledged that NDMA or</p> <p>11 NDEA could cause cancer in humans, that's something you</p> <p>12 certainly would have wanted to see; right?</p> <p>13 MR. INSOGNA: Object to form. Assumes</p> <p>14 facts.</p> <p>15 A. I would want to see that, yes. Would that</p> <p>16 have played a role in my decision, what they thought?</p> <p>17 Not necessarily.</p> <p>18 BY MR. SLATER:</p> <p>19 Q. What if the "they" was a toxicologist</p> <p>20 retained by one of the companies to analyze this exact</p> <p>21 question?</p> <p>22 Would that have been important to you to</p> <p>23 see?</p> <p>24 MR. INSOGNA: Same objection.</p>

<p style="text-align: right;">Page 114</p> <p>1 A. If they had done an analysis, sure, I 2 would like to see what they showed -- 3 Q. What if it was the testimony of a 4 corporate witness who was speaking for the company on 5 that specific question of the risks of the NDMA and 6 NDEA in the valsartan and that person acknowledged that 7 there was a risk to humans of cancer? 8 Would you have wanted to see that? 9 MR. INSOGNA: Same objections. 10 A. Sure. 11 BY MR. SLATER: 12 Q. For example, if there were witnesses who 13 testified for one or more of the manufacturers who 14 agreed that NDMA and NDEA are probable human 15 carcinogens, if they said that in sworn testimony 16 speaking for the company, would you have wanted to see 17 that in forming your opinions? 18 MR. INSOGNA: Same objections. Assumes 19 facts. Do you have a document you want to show him, 20 counsel? 21 BY MR. SLATER: 22 Q. Please answer. 23 MR. INSOGNA: You can answer. 24 A. Sure, I would like to see that, and I</p>	<p style="text-align: right;">Page 116</p> <p>1 change anything that we already know. 2 Q. Just so I make sure that it's clean for 3 both of our benefit, you don't disagree with the 4 finding by IARC that NDMA and NDEA are probable human 5 carcinogens? 6 That statement in and of itself you don't 7 disagree with; right? 8 MR. INSOGNA: Object to form. Asked and 9 answered. 10 A. Yeah, I just answered that question. So 11 yes, I don't think that I disagree with that, with the 12 understanding I also mentioned, is that that doesn't 13 take into account the dose and the duration, which I 14 think is an important thing to consider here in this 15 particular question. 16 BY MR. SLATER: 17 Q. Putting aside dose and duration, which 18 would become relevant to determining whether a 19 particular person claiming a particular cancer actually 20 got cancer in whole or in part from the exposure to the 21 NDMA in the valsartan pills -- 22 I think that's what you're driving at; 23 right? 24 A. No.</p>
<p style="text-align: right;">Page 115</p> <p>1 don't think what you just said would be anything 2 different than what I just already said earlier, and 3 that's been said by many experts, that it's 4 acknowledged that it's a probable human carcinogen. 5 It's not a definite human carcinogen. 6 So what you're telling me right now is not 7 changing anything that we already know, but would I 8 want to see the document? Of course. 9 BY MR. SLATER: 10 Q. And when you refer to the probable human 11 carcinogen, that's the finding IARC made; right? 12 A. Right. 13 Q. And you don't disagree with IARC; right? 14 A. Well, I think we're going to get into it, 15 but maybe this is a good time to say. IARC is telling 16 us that those -- that NDMA and NDEA are probable human 17 carcinogens, but that doesn't take into account the 18 dose or the duration of the exposures to these agents 19 and that they -- ultimately they're an extrapolation 20 from animal models, from rat models, with a lot of 21 limitations that are quite conservative. 22 But yes, I mean, I think we've established 23 that IARC said that, and so this other document you're 24 talking about so far from what you told me wouldn't</p>	<p style="text-align: right;">Page 117</p> <p>1 MR. INSOGNA: Go ahead. 2 A. No, that's not -- I'm not talking about 3 that at all. I'm just saying that because it's listed 4 as a probable carcinogen is one thing, but do have to 5 understand that all that's saying is that at some dose 6 level and for some duration that it's probably 7 carcinogenic in humans. 8 Again, it's only probably and not 9 definitively because it hasn't been shown in humans to 10 have that, yet it has in some animal models, at huge 11 doses, by the way, and for long durations that are 12 astronomically higher than what's in this case, which 13 is why I called it trace exposure in this case. 14 BY MR. SLATER: 15 Q. Okay, I see where our disconnect is. I'll 16 try to ask the question artfully. You -- rephrase. 17 You agree with IARC that NDMA and NDEA are 18 probable human carcinogens, putting aside the dose or 19 duration of use or exposure -- putting that aside, you 20 don't disagree that those substances are probable human 21 carcinogens; correct? 22 MR. INSOGNA: Form. Asked and answered. 23 A. If you're asking me to put those other 24 considerations aside, then yes, officially the IARC</p>

<p>Page 118</p> <p>1 classifies these as 2A.</p> <p>2 BY MR. SLATER:</p> <p>3 Q. And you don't disagree with that; right?</p> <p>4 A. No.</p> <p>5 Q. Your answer was no?</p> <p>6 A. No, I don't disagree with that.</p> <p>7 Q. Sorry. Sometimes with the delay I get a</p> <p>8 click on my -- it's totally on my end. I just missed</p> <p>9 it. I'm sorry.</p> <p>10 [Discussion off the record.]</p> <p>11 BY MR. SLATER:</p> <p>12 Q. Let's go back to the amended list of</p> <p>13 materials considered, the regulatory guidances and</p> <p>14 documents. First there's a heading that says</p> <p>15 publicly-available documents.</p> <p>16 Do you see that?</p> <p>17 A. Yes.</p> <p>18 Q. Have you read or reviewed any of those</p> <p>19 materials before you were retained in this case?</p> <p>20 A. No.</p> <p>21 Q. In terms of forming your own opinions in</p> <p>22 this case, are you relying on the regulatory</p> <p>23 information to form your own scientific conclusion, or</p> <p>24 is this more background information on what occurred</p>	<p>Page 120</p> <p>1 A. I didn't do calculations to show what I</p> <p>2 would perceive as being an acceptable intake. I've</p> <p>3 read the toxicologists on both sides, and as I</p> <p>4 mentioned I think earlier, I added a paper that I found</p> <p>5 after from Fitzgerald, I think, about other ways of</p> <p>6 determining acceptable intakes.</p> <p>7 And so I did take that into account and I</p> <p>8 think even in my report you can see where I discussed</p> <p>9 the acceptable intake from the FDA standpoint and some</p> <p>10 of the limitations of it.</p> <p>11 Q. You didn't do an independent assessment of</p> <p>12 the intake levels for the FDA and form an opinion that</p> <p>13 those levels were unreasonable?</p> <p>14 I didn't see that opinion in your report.</p> <p>15 I just want to make sure I didn't miss it.</p> <p>16 MR. INSOGNA: Objection. Compound.</p> <p>17 BY MR. SLATER:</p> <p>18 Q. I'll ask it differently because counsel</p> <p>19 objected. He -- just like I have to be evenhanded, I</p> <p>20 have to assume I could ask a bad question every so</p> <p>21 often.</p> <p>22 I didn't see an opinion in your report</p> <p>23 that you disagree with the acceptable intake levels</p> <p>24 established by the FDA.</p>
<p>Page 119</p> <p>1 and what the regulator said?</p> <p>2 How do you mix that into your analysis? I</p> <p>3 want to understand how it fit into your methodology.</p> <p>4 MR. INSOGNA: Object to form. Compound.</p> <p>5 A. It was obviously background to understand</p> <p>6 the timeline of what happened and what the FDA's</p> <p>7 positions were along the way. I actually referenced a</p> <p>8 lot of their statements.</p> <p>9 And so with your question about how to</p> <p>10 formulate my opinion, a lot of what they made mention</p> <p>11 and that I point out in my report does have some weight</p> <p>12 in terms of my understanding of things in terms of the</p> <p>13 risk, the risk assessment that they had made based on</p> <p>14 these putative exposures, et cetera. All of their</p> <p>15 statements did play a role into my opinion.</p> <p>16 BY MR. SLATER:</p> <p>17 Q. In that context, the FDA, for example,</p> <p>18 established acceptable -- what they called acceptable</p> <p>19 intake limits.</p> <p>20 You're aware of that obviously; right?</p> <p>21 A. Yes.</p> <p>22 Q. You didn't do an independent assessment</p> <p>23 and form an opinion as to whether or not those figures</p> <p>24 the FDA adopted are reasonable or not; right?</p>	<p>Page 121</p> <p>1 There isn't such an opinion in your</p> <p>2 report? Am I correct?</p> <p>3 A. I don't know verbatim what I put about</p> <p>4 that in my report, but if you want my opinion I can</p> <p>5 tell you right now, but I don't remember what the</p> <p>6 actual detail -- how I mention that or worded it in my</p> <p>7 report in terms of that particular threshold level.</p> <p>8 Q. What I want to do is -- part of what I'm</p> <p>9 doing is you understand the purpose of your report</p> <p>10 obviously is to give us notice before your deposition</p> <p>11 of what your opinions are.</p> <p>12 You know that; right?</p> <p>13 A. Yes.</p> <p>14 Q. So my goal is not to expand into a bunch</p> <p>15 of other things and ask you a bunch of things you</p> <p>16 didn't think about. My goal is to try to stay within</p> <p>17 your report because those are the opinions we've been</p> <p>18 told about.</p> <p>19 You understand that; right?</p> <p>20 A. Yes.</p> <p>21 Q. In the report itself, I did not see an</p> <p>22 opinion where you said that the FDA acceptable intake</p> <p>23 levels are unreasonable for some reason and that</p> <p>24 different levels should have been adopted and here's</p>

<p style="text-align: right;">Page 122</p> <p>1 why. I didn't see such an analysis. 2 Did I miss it, or is it not there? 3 A. I don't think I did that analysis 4 explicitly in the report. 5 Q. For purposes of your opinions, did you 6 accept -- well, let me ask it this way. 7 You said that you've seen some studies 8 where different people in some articles calculated 9 different levels or different approaches to looking at 10 acceptable levels, but putting that aside, you accepted 11 the FDA levels for purposes of your analysis; is that 12 correct? 13 MR. INSOGNA: Object to form. Misstates 14 testimony. 15 A. Well, no. I mean, I think that that's why 16 I was getting a little confused what you're asking -- 17 is that I pointed out from the dietary studies, for 18 example, the exogenous and endogenous known exposures 19 that we were talking about earlier, which are way 20 higher than this supposed acceptable rate that the FDA 21 is saying, and I point that out here. 22 So intuitively that means implicitly that 23 clearly it's lower than what we're always exposed to on 24 an everyday basis, but also point out that it's a</p>	<p style="text-align: right;">Page 124</p> <p>1 Q. Well, I'm in the next section now, 2 actually, so I want to make sure we're clear. On Page 3 2 there's a new heading, company documents produced. 4 Do you see that? 5 A. Oh. Sorry. I'm looking at materials 6 considered at the top of that page, so now in the 7 bottom, yes, those were definitely ones that were 8 provided to me. 9 Q. And again, to the extent that defense 10 counsel had in their possession company documents that 11 one would objectively say, "Well, that actually 12 supports the position that these substances could cause 13 cancer in humans," you would have wanted to see those 14 so you could take that into account; right? 15 MR. INSOGNA: Objection. Assumes facts. 16 A. I think I answered that I think all data 17 are good to consider. Whether or not they would 18 actually play a role any differently in an opinion is a 19 different question, though -- until I saw the data. 20 BY MR. SLATER: 21 Q. Assume for this question that there is 22 deposition testimony and documents you were not shown 23 that an objective viewer would look at and say, "Well, 24 that clearly supports the plaintiff's position in this</p>
<p style="text-align: right;">Page 123</p> <p>1 conservative estimate that was extrapolated from a rat 2 model in a linear fashion that was using doses that 3 were really high doses compared to what we actually 4 know are exposed to on a daily basis and also the 5 question at hand in the trace impurities. So I did 6 point that out in a number of places in my report. 7 BY MR. SLATER: 8 Q. You did not actually perform a risk 9 assessment where you took into account all the various 10 data points in the animal studies, the dietary studies, 11 et cetera, and perform your own analysis and establish 12 what would be an appropriate alternative acceptable 13 intake level? 14 That's not something you did; right? 15 MR. INSOGNA: Object to form. Compound. 16 A. I didn't do that, no. 17 BY MR. SLATER: 18 Q. On Page 2 of this document we're looking 19 at, there's a heading company documents produced, and 20 those would have all been provided to you by counsel; 21 correct? 22 A. Yes. Some of them I found on my own, like 23 the FDA statements, as we talked about. But yeah, some 24 of -- they were all provided by counsel.</p>	<p style="text-align: right;">Page 125</p> <p>1 case that the NDMA and NDEA could cause cancer in 2 humans at the dosages taken in the valsartan pills." 3 I'd like you to assume that exists. 4 I'd also like you to assume it was not 5 provided to you. If that's true, would you agree with 6 me that subject to seeing that information, your 7 opinions could change if you were to see that 8 information because you don't have it available? 9 Would you agree with that? 10 MR. INSOGNA: Objection. Assumes facts, 11 incomplete hypothetical, argumentative, misstates 12 testimony. 13 A. I would have to see what it is that you're 14 talking about to make an appropriate answer to that 15 question. 16 BY MR. SLATER: 17 Q. Looking now at Page 4 of this document, 18 the heading literature. 19 Is it your testimony that you read every 20 one of these articles cover to cover? 21 A. No, I didn't read them all cover to cover. 22 Q. Just -- 23 A. Some of them are skimming through, looking 24 at abstracts, looking at main findings. Other of them,</p>

<p style="text-align: right;">Page 126</p> <p>1 I did read cover to cover multiple times.</p> <p>2 Q. And just to be clear and you could confirm</p> <p>3 this just so we have it for the record. This section</p> <p>4 headed literature starts on Page 4 and goes all the way</p> <p>5 to Page 39, about three-quarters of the way down the</p> <p>6 page; right?</p> <p>7 A. Yes.</p> <p>8 Q. If the counsel for the defense was aware</p> <p>9 of literature that objectively viewed would cut against</p> <p>10 the position that you've taken in your report, you</p> <p>11 would have wanted to be given that literature by</p> <p>12 defense counsel so you could take it into account in</p> <p>13 forming your opinions; correct?</p> <p>14 MR. INSOGNA: Objection. Assumes facts.</p> <p>15 Argumentative. Incomplete hypothetical.</p> <p>16 A. If I hadn't already found it and if it</p> <p>17 wasn't in the actual plaintiff experts' reports, which</p> <p>18 presumably such documents would be there and relied</p> <p>19 upon, then if everyone missed it except for defense</p> <p>20 counsel, sure, I would like to see it.</p> <p>21 BY MR. SLATER:</p> <p>22 Q. Well, this list of literature is the --</p> <p>23 well, let me ask this question. Let me understand</p> <p>24 something. We'll take a step back.</p>	<p style="text-align: right;">Page 128</p> <p>1 always in the mind frame from that sort of coming from</p> <p>2 that framework, is that I'm trying to be concise and</p> <p>3 not include every single topic and every single</p> <p>4 statement having heavily-referenced articles.</p> <p>5 Q. In the course of your report you cited</p> <p>6 with specific reference numbers certain literature. If</p> <p>7 there's other literature in this list of literature</p> <p>8 that was not specifically referenced with a numerical</p> <p>9 reference number, does that mean that it's something</p> <p>10 you looked at for background but it's not something</p> <p>11 that you found to be so significant that you needed to</p> <p>12 specifically cite to it in the report?</p> <p>13 MR. INSOGNA: Object to form.</p> <p>14 A. Yes, like the example that came up earlier</p> <p>15 where one of the articles that I came across and I</p> <p>16 read, it wasn't as pertinent to my actual opinion. I</p> <p>17 had read it, but it wasn't something that I relied on</p> <p>18 or discussed, and that was that JAMA article; right?</p> <p>19 But when you asked me about it, then,</p> <p>20 yeah, I know about it because I came across a lot of</p> <p>21 things as I was filtering through what I thought was</p> <p>22 necessary to formulate my opinion here.</p> <p>23 BY MR. SLATER:</p> <p>24 Q. So with regard to the items on this list</p>
<p style="text-align: right;">Page 127</p> <p>1 In the report you have references,</p> <p>2 numbered references?</p> <p>3 A. Yes.</p> <p>4 Q. And the purpose of that is so that if you</p> <p>5 said something in the report and you're specifically</p> <p>6 relying on a specific document or a specific study or</p> <p>7 piece of literature, you're telling us that's where</p> <p>8 this comes from; right?</p> <p>9 A. Yes and no. Sometimes it's -- especially</p> <p>10 in the background sections of my report or the</p> <p>11 backgrounds of cancer where much of what I was saying</p> <p>12 is common knowledge in my field, but to provide some</p> <p>13 references in case somebody wanted to go and look at</p> <p>14 it, one or two token references on a topic, certainly</p> <p>15 not an exhaustive reference for each topic is in this</p> <p>16 report or there would a billion references here. And</p> <p>17 so yes and no.</p> <p>18 Sometimes it's more of whoever's reading</p> <p>19 this can go and look more at detailed information from</p> <p>20 that discussion if they wanted to, which is a lot of</p> <p>21 how we do our references and publications.</p> <p>22 And sometimes we have limit -- most of the</p> <p>23 time we have a limitation in terms of the number of</p> <p>24 references one can get included in a paper, and so I'm</p>	<p style="text-align: right;">Page 129</p> <p>1 of literature that are not specifically referenced in</p> <p>2 your report, again, that would be general background</p> <p>3 information as opposed to something that you thought</p> <p>4 was so important to your opinion that you needed to</p> <p>5 actually reference it specifically? Is that correct?</p> <p>6 MR. INSOGNA: Object to form. Misstates</p> <p>7 testimony.</p> <p>8 A. I'd have to look at the exact example</p> <p>9 you're looking at to be certain because sometimes maybe</p> <p>10 it did influence what I was thinking, but I didn't</p> <p>11 actually put the number here in the reference. But</p> <p>12 overall I think it would be safe to say that the things</p> <p>13 that are referenced here are the ones that are the</p> <p>14 emphasized reports that were relied upon for generating</p> <p>15 my opinion.</p> <p>16 BY MR. SLATER:</p> <p>17 Q. Looking now at Page 39 of this document,</p> <p>18 there's a heading that says records of bellwether</p> <p>19 plaintiffs. And I assume what that means is that</p> <p>20 you're been provided some of the records of some of the</p> <p>21 bellwether plaintiffs and you're evaluating specific</p> <p>22 causation in some cases as well.</p> <p>23 Is that a fair assumption?</p> <p>24 A. No, they were provided to me. I looked</p>

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1 at -- this was a long time ago when they were first
 2 given to me back it looks like in April, and I was sort
 3 of told that these are -- just to have a full sort of
 4 file of this, but you're not -- we're not going to be
 5 doing specific patient cases at this point. So I
 6 didn't put a lot of emphasis on reading that to great
 7 detail.
 8 Q. Am I correct you didn't rely on the
 9 records of bellwether plaintiffs, as you've listed
 10 those materials here in forming those opinions in this
 11 case?
 12 A. Yeah, I didn't look at them or use those
 13 to make opinions here in this in any significant way.
 14 Q. Could you go to Page 52, please? On Page
 15 52 there's a heading postmarketing periodic safety
 16 reports.
 17 Do you see that?
 18 A. Yes.
 19 Q. Why did you include those documents that
 20 come under that heading? What was the point of that?
 21 A. I think as mentioned earlier, I think it's
 22 just to have a complete file to look at. As you were
 23 alluding to earlier, to have as much of the information
 24 available to evaluate along the way what was being

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1 documented.
 2 Q. Did you ask for these documents, which as
 3 we can see in the subheadings are various ANDAs --
 4 ANDA?
 5 Did you ask for that, or was that just
 6 provided to you by counsel?
 7 A. I can't remember.
 8 Q. Did you rely on those documents in any
 9 specific way in forming your opinions in this report?
 10 A. Not in a significant way. I looked at
 11 them. I think that they have limited utility in the
 12 questions that were being asked of me.
 13 Q. I didn't see them cited for any
 14 proposition or to support any of your opinions. Right?
 15 A. Yeah. Like I said, I think I just said
 16 that they had limited utility in forming my opinions.
 17 Q. Looking at the Page 53, there's a heading
 18 that says miscellaneous.
 19 A. Which page? Excuse me.
 20 Q. Last page, Page 53.
 21 A. Yes.
 22 Q. It says miscellaneous.
 23 A. Yes.
 24 Q. The first section under miscellaneous is

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1 all plaintiff diagnosis and treatment report.
 2 Do you know what that is?
 3 A. I think that must be related a little bit
 4 to the other section that was about the actual patient,
 5 which I didn't look at in great detail.
 6 Q. The next line says, "All plaintiff
 7 diagnosis and treatment report additional data."
 8 Would that be the same answer?
 9 A. Yes.
 10 Q. The third line says, "All materials cited
 11 or referenced in my expert report and attachments."
 12 Do you know why that's listed there?
 13 A. Just to be explicit that all of the things
 14 in my report are here. Certainly -- in case one was
 15 missed, maybe to ensure that -- that would not be
 16 intentional.
 17 Q. So that means if something was referenced
 18 in the actual body of the report but didn't find its
 19 way into this document, Exhibit B, you're saying I'm
 20 relying on it if it's stated in my report, but I didn't
 21 get it onto this list?
 22 A. That's what that sounds like, yes.
 23 Q. Or I read it? May not be relied on, but I
 24 read it; right?

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1 A. Sure. Yes.
 2 Q. The last line here says, "This list
 3 includes items plaintiffs' experts relied upon. By so
 4 doing, defendants and this expert are not waiving any
 5 arguments or objections related to admissibility."
 6 Do you know why that line was included?
 7 MR. INSOGNA: Object to form.
 8 A. I don't.
 9 MR. SLATER: Counsel, this is probably
 10 another good break point, and it's 1:30 -- or 12:30
 11 where you are. I don't know -- it's probably a decent
 12 point to break and eat if you want to eat. Want to go
 13 off the record and talk about it?
 14 MR. INSOGNA: Yeah, we can go off the
 15 record and discuss it.
 16 THE VIDEOGRAPHER: We're going off the
 17 record at 12:24 PM.
 18 [A recess was taken.]
 19 THE VIDEOGRAPHER: We are back on the
 20 record at 1:20 PM.
 21 MR. SLATER: I just realized why I keep
 22 writing down the wrong time, because you keep telling
 23 the time Central Time.
 24 BY MR. SLATER:

<p style="text-align: right;">Page 134</p> <p>1 Q. Okay. All right. I overlooked one thing 2 I wanted to ask you about earlier, so let's just cover 3 that, and then we'll go back into some other things. 4 Have you consult -- new question. 5 Have you consulted for pharmaceutical 6 companies over the years? 7 A. Yes. 8 Q. When did you first start consulting for 9 the pharmaceutical companies? 10 A. Probably around 10 years ago, 11 years 11 ago, when I joined faculty at the University of 12 Chicago. 13 Q. What do the consulting activities relate 14 to? I'm not talking about grants for studies. I'm 15 putting that to the side. 16 Other than any actual grants for studies, 17 what does your consulting work for the pharmaceutical 18 industry involve? 19 A. Most of the time it's advising in terms of 20 novel therapeutic agents and how to develop them or 21 where to develop them and looking at some of their data 22 and giving opinions as to what the utility user is not 23 in -- in the future of treating that cancer. That's -- 24 most of that is consulting to that degree.</p>	<p style="text-align: right;">Page 136</p> <p>1 things. And so looking over the years, it has probably 2 gone up each year a little bit, but on average it's 3 over the last 10 years maybe \$20,000, \$25,000 a year, 4 roughly, as an estimate as to how much has been 5 provided to me as honoraria for various consulting that 6 I've done. 7 BY MR. SLATER: 8 Q. We did a little research and came up with 9 some online information. As you said, it is available. 10 And going backwards, the data I found showed payments 11 of \$37,000 approximately for the activities that we 12 just talked about in 2020. 13 Does that sound correct? 14 A. Yeah, that sounds in line. 15 Q. And I have a number in 2019 of \$41,611.60. 16 Does that sound correct? 17 A. Sounds like it could be correct. 18 Q. In 2018, I have the number of \$59,127.48. 19 Does that sound correct? 20 A. Sounds like it's getting higher than 21 average, but one thing I'll point out is that sometimes 22 things like research funding to clinical trials gets 23 into that database and inaccurately lists amounts that 24 come to me directly.</p>
<p style="text-align: right;">Page 135</p> <p>1 Q. What else? 2 A. In a smaller subset, I've been asked to be 3 a speaker for certain products, and I will -- I have 4 done that, and I do that much less often, but -- and 5 usually for therapeutic drugs that are for specific 6 treatments for gastroesophageal cancer, which is my 7 sub-specialty. 8 Q. Do you have an estimate of what you've 9 been paid either annually or in total by the 10 pharmaceutical industry for things like promotional or 11 speaking, consulting, travel and lodging, 12 reimbursements for food and beverage, all those things 13 taken together? Do you have any estimate of what 14 that's -- what those payments have been to you over the 15 years? 16 A. Yeah, those are -- should be online 17 through the open Sunshine Act policy. 18 Q. Do you have an understanding or an 19 estimate of what those amounts have been that you've 20 been paid? 21 MR. INSOGNA: (Inaudible.) 22 A. Yeah, I mean, I'd have to look back, but I 23 can tell you probably over the years, as I have become 24 more senior and involved, I get asked to do more</p>	<p style="text-align: right;">Page 137</p> <p>1 But regardless, it is probably, as I 2 mentioned, on average -- over the last few years 3 \$25,000 as an average over the full 10 to 11 years. 4 Some years more, some years less. More recent years -- 5 Q. I can tell -- yeah, I can tell you that 6 they break out -- this is the open payments website 7 from the U.S. government, and they actually break out 8 research funding as a separate category. So I'm just 9 limiting it to the nonresearch funding category. 10 A. Right, and what I'm saying is that there 11 has been occasion when I was looking at that and it 12 didn't make sense and it wasn't accurate and I had to 13 have them remove it in the past. 14 But regardless, I'm not sure about that 15 either. It sounds like it's still within line of my 16 actual activities with them as a consultant. So -- 17 Q. So the number that we had left off with 18 was for 2017, \$78,534.93, and they count 82 payments 19 that year. 20 Does that sound accurate? 21 A. 2018? 22 Q. 2017. 23 A. Yeah, that -- some of those, like you had 24 already pointed out, are for travel. So I think in</p>

<p style="text-align: right;">Page 138</p> <p>1 that year was the year that I went to Europe on a 2 business flight. So more than like 15 percent of that 3 is just from that one flight. 4 Q. The Dollars For Docs website, which gets 5 its information, as you know, from the government data, 6 for 2017 has your travel and lodging as \$14,196; your 7 promotional and speaking payments at \$15,230; your 8 consulting at \$37,350; accredited training, \$9,800; and 9 then the food and beverages, \$1,953. 10 Do those numbers sound accurate? 11 A. That sounds right. 12 Q. For 2018, the Dollars for Docs website had 13 promotional and speaking as \$37,933; consulting as 14 \$7,725; travel and lodging at \$6,640; and food and 15 beverage at \$1,290. 16 Does that sound accurate? 17 A. On the surface, it sounds similar, yeah, 18 to the previous year, and accurate. 19 Q. When there's reference in these documents 20 to promotional speaking, does that mean when you're 21 speaking on behalf of the company and they're paying 22 you as a speaker? 23 A. It was what I was referring to earlier, 24 where I'll speak on one of their products to a group of</p>	<p style="text-align: right;">Page 140</p> <p>1 arranged for and completely organized by the 2 pharmaceutical company; right? 3 A. Not always. Sometimes they are through a 4 third independent party and offer continuing medical 5 education, for example. And so sometimes they are not 6 organized by the company themselves. 7 Q. Well, the promotional speaking where the 8 marketing department -- well, let me ask -- let me 9 rephrase. 10 The promotional speaking wouldn't be 11 continuing education; that would be promotional -- 12 where you're promoting the product; right? 13 A. Yes, for ones that you're referring to, 14 then they would be organized by the pharmaceutical 15 company. 16 Q. And you would be interacting with people 17 from the marketing department; right? 18 A. I believe so. They're commercial 19 marketing, sales. 20 Q. They arrange for the doctors to attend and 21 they bring them to the event; right? 22 A. Yes. 23 Q. And you certainly understand that the 24 reason they're retaining you to speak is because</p>
<p style="text-align: right;">Page 139</p> <p>1 physicians, usually, or health care professionals on 2 details of that product. 3 That usually is an FDA-approved product 4 that has a topic of the actual studies that led to the 5 FDA approvals and a balanced representation of the 6 risks and benefits of that drug. 7 And so they're like viewed as a -- 8 educational presentations to physicians in the 9 community that aren't as aware of these new drugs that 10 are coming through to bring awareness for them. 11 Q. They're viewed as educational, they're 12 also viewed by the company as marketing events because 13 they're hoping that the doctors you're speaking to will 14 utilize the product that you're talking about; right? 15 MR. INSOGNA: Object to form. 16 A. They are commercial events from their 17 perspective, and I think that's obviously why they do 18 it, why I do it. I only do talks for drugs that I use 19 and that I believe are beneficial to patients with 20 cancer, and I view it as a way to communicate and meet 21 new physicians and relate that information of that 22 drug. 23 BY MR. SLATER: 24 Q. These speaking engagements -- they're</p>	<p style="text-align: right;">Page 141</p> <p>1 they're hopeful that when you speak about their product 2 that the doctors in attendance will choose to purchase 3 the product or prescribe the product that you're 4 speaking on, as opposed to competitors, for example; 5 right? 6 MR. INSOGNA: Object to form. Calls for 7 speculation. 8 BY MR. SLATER: 9 Q. You understand that's what the marketing 10 people who hire you want to happen; right? 11 MR. INSOGNA: Object to form. Calls for 12 speculation. 13 A. I think that that is true. 14 BY MR. SLATER: 15 Q. Now, let's go back to your report, if we 16 could. And I think probably we should use the most 17 recent version, the August 27, 2021, version. 18 A. Yes. 19 Q. So I'm going to walk through the report a 20 little. 21 The first section is the biography and 22 qualifications, and that's just an overview of your 23 background; correct? 24 A. Yes.</p>

<p style="text-align: right;">Page 142</p> <p>1 Q. The second section, which starts on Page 2 3, titled scope and summary of opinions, is an outline 3 of the information that's found in the report going 4 forward; right? 5 A. Yes. 6 Q. Section 3 is titled introduction to 7 cancer, and that's found on Page 6. 8 Do you see that? 9 A. Yes. 10 Q. Let's go through this a little bit. 11 This -- we'll rephrase. 12 This introduction to cancer section is 13 really just a general overview of certain concepts 14 related to what cancer is and how it occurs in the 15 body; right? 16 A. Yes. 17 Q. At the bottom of Page 7, you state, 18 "Environmental factors that contribute to the cause of 19 cancer have been described and can be specific to 20 certain cancer types. Environmental factors include 21 aspects of lifestyle, economic, and behavioral 22 exposures. Poor diet, inactivity, and 23 sedentary lifestyle, and obesity, and metabolic 24 syndrome have each been associated with carcinogenesis.</p>	<p style="text-align: right;">Page 144</p> <p>1 as it also tracks and closely associates with other 2 cancer-related risk factors of smoking, alcohol use, 3 obesity, diabetes, diet, and other factors"? 4 A. Yes. 5 Q. And then you say, "After adjusting for 6 these known cancer risk factors, however, hypertension 7 is also potentially an independent cancer risk factor 8 in a number of tumor types, including renal, 9 colorectal, breast, esophageal, liver, and uterine 10 cancers." 11 Correct? 12 A. Correct. 13 Q. And when you say potentially, you're 14 saying it's possible; right? 15 A. Right. 16 Q. Did you say yes? 17 A. Yes, I said right. 18 Q. Okay. 19 A. I said that -- I can expand on that, that 20 the data that looked at those studies concluded that 21 it's after adjusting for all the known and associated 22 confounders, which are listed there, that there 23 remained what appeared to be an association, but that's 24 why it's still potentially associated, because despite</p>
<p style="text-align: right;">Page 143</p> <p>1 Some specific foods are linked to specific cancers." 2 So going through what you just read, that 3 again is an overview of the fact that there's things 4 that we're exposed to in our day-to-day lives that can 5 cause or contribute to cancer; correct? 6 MR. INSOGNA: Object to form. 7 A. As an overview, there are a lot of 8 different etiologies of cancer, and I list some of the 9 main categories there. 10 BY MR. SLATER: 11 Q. On Page 8, the second full paragraph says, 12 "Broadly speaking, any factor that may alter one's DNA 13 sequence could contribute to carcinogenesis and the 14 ultimate development of cancer and could be referred to 15 as a carcinogen." 16 Correct? 17 A. That's what that says, yes. 18 Q. Just -- rephrase. 19 Looking at the first paragraph on Page 8, 20 you talk about hypertension as being associated with 21 increased cancer risk and cancer mortality. 22 Correct? 23 A. Yes. 24 Q. And you state that this is "particularly</p>	<p style="text-align: right;">Page 145</p> <p>1 trying to adjust for confounders, there's always 2 residual confounding that's difficult to measure and 3 adjust for. 4 So either way, the point I was making here 5 is that whether it's actually associated independently 6 or because it's associated with all the other things 7 that we know are associated with cancer, hypertension 8 is associated with cancer. 9 Q. Again, when you say hypertension's 10 associated with cancer, as we just read through, my 11 understanding was that it's something that is seen but 12 there's these other independent factors that you have 13 to adjust for. 14 Do I understand that correctly? 15 A. And -- yes, and after adjusting for them 16 in some reports that I reference here there was 17 residual association with hypertension and cancer, 18 suggesting that there's a potentially independent 19 association with hypertension even aside of all the 20 other things that we're talking about here. 21 Q. And the studies that you cited there -- 22 you're saying there was a potential association shown. 23 Is that because the association didn't 24 achieve statistical significance?</p>

<p style="text-align: right;">Page 146</p> <p>1 A. No, I think that's -- that's scientific 2 language to say that we have to be cautious with our 3 interpretations of studies, and finding an association 4 in a given analysis is not definitive from one look, 5 and so a conservative way to say that there's still 6 potential association that merits further 7 investigation, for example. 8 Again, my point there was to suggest that 9 whether it's independently associated or associated by 10 proxy, it's associated with cancer -- hypertension. 11 Q. Just for the record, I'm not going through 12 Section 4, the cancer prevention, screening, and 13 incidence section, because I read that as going to the 14 medical monitoring, so I assume we should skip that. 15 Then we have Section 5 on Page 12. 16 Cancer -- actually, it should be -- yes. Looking -- 17 new questions. 18 Looking at Page 12 at the top, cancer 19 symptoms, diagnosis, and staging, Section 5. 20 Does that section relate specifically in 21 any way to the question of whether or not the NDMA or 22 NDEA can cause cancer in humans? 23 MR. INSOGNA: Object to form. 24 BY MR. SLATER:</p>	<p style="text-align: right;">Page 148</p> <p>1 quality of life as long as possible, I often say this 2 is not the time to stop, you might as well enjoy life. 3 So -- honestly. So that's -- in some cases, no, we 4 don't. 5 Q. And looking at Section 7, posttreatment 6 cancer surveillance, that again is medical monitoring, 7 so I'm not going to get into that. Okay. 8 Looking now at Section 8, which starts on 9 Page 13. There's a discussion of specific cancers, and 10 it goes all the way through Page 29. 11 A. Yes. 12 Q. The specific discussion of these various 13 cancers is background information and is not 14 specifically significant to your opinions as to whether 15 or not NDMA and NDEA can cause or contribute to cancer 16 in humans; correct? 17 MR. INSOGNA: Object to form. Compound. 18 A. I think the information is impertinent 19 that's in here, from a couple of standpoints. One is 20 the -- it talks about the incidence of cancer. And -- 21 as a whole, but also each one of these. And also the 22 risk factors that one has to consider, and how common 23 these cancers can be, based on how common these risk 24 factors are.</p>
<p style="text-align: right;">Page 147</p> <p>1 Q. Or is it just background information? 2 A. No, it's background information. 3 Q. Looking at Section 6, cancer treatment. 4 Is that also background information? 5 MR. INSOGNA: Object to form. 6 A. Not all of it. As you can see in Page 13, 7 the last paragraph of Section 6 is discussing the 8 notion that these -- the NDMA and NDEA identified in 9 valsartan could potentially affect how one treats the 10 cancer or how one's cancer responds to treatment, and 11 so I pointed out that there's no such evidence that it 12 has any impact on how one approaches cancer treatment 13 in any way. 14 BY MR. SLATER: 15 Q. When people are undergoing treatment for 16 lung cancer, is it suggested to them that they should 17 stop smoking? 18 A. We suggest that to everybody, because 19 smoking can make things worse even in the setting of 20 when you already have cancer. So we would always say 21 that, but in fact in many cases, like with my patients 22 who we're treating with end-of-life cancers, terminal 23 cancers, who actually at that point the treatment is 24 with the intention to palliate them and to optimize</p>	<p style="text-align: right;">Page 149</p> <p>1 So I think that's a pertinent background 2 understanding when you're talking about now another 3 putative variable that might be associated with cancer 4 risk is to put that in a context of what's already 5 happening and why and to take that into account. 6 But I don't -- I think it's more than just 7 background. I think it's part of an important 8 consideration. And these things come up again I think 9 later in the later sections, when we're talking about 10 some of the FDA referenced risks of these agents in 11 valsartan, and putting that in context of what the base 12 rate and risk is of getting cancer in society. So I 13 think that that's important to consider. 14 BY MR. SLATER: 15 Q. How does the incidence of these cancers 16 specifically relate to the opinions that you're 17 offering as to whether or not NDMA and NDEA can 18 increase one's cancer -- risk of cancer? 19 MR. INSOGNA: Object to form. Misstates 20 testimony. 21 A. I think they're important to consider when 22 looking at the risk or lack thereof of something else 23 on top of what we already understand. 24 But in terms of what the risk is, if any,</p>

<p style="text-align: right;">Page 150</p> <p>1 of the putative exposures to valsartan-containing drugs 2 that had impurities, that's not actually pertinent to 3 the analysis that I did, in terms of the 4 epidemiological analysis, dietary studies, the 5 occupational exposures, and the animal data, per se, in 6 terms of me making an opinion whether or not there is 7 added risk. 8 But I -- what I was alluding to was if 9 we went to the next section, where the FDA is 10 indicating sort of like the one -- above the accepted 11 daily intake and what the risk is for a patient taking 12 it at that daily intake for 70 years, taking that into 13 account, you must understand what the basal incidence 14 of cancers are to put that into context. 15 BY MR. SLATER: 16 Q. Whatever the baseline incidence of cancer 17 is, either NDMA and NDEA people are exposed to 18 day-to-day either is contributing to that incidence 19 level or not; right? 20 MR. INSOGNA: Object to form. 21 Argumentative. 22 A. Can you rephrase that? 23 BY MR. SLATER: 24 Q. Yeah. You spoke about the cancer</p>	<p style="text-align: right;">Page 152</p> <p>1 going to get to when we talk about the epi data, in 2 terms of the additional contribution of these drugs, 3 does it cause any extra risk. 4 So you need to sort of know what the basal 5 risk is to begin with, from all the known associations 6 and mostly unknown reasons why patients get cancer. 7 Q. There's no such study that was set up to 8 measure in a general sense the increased risks of 9 cancer in general as of 2012; right? There was the 10 studying you're talking are Gomm and Pottgard, where 11 they compared different sets of people in the cohort; 12 right? 13 A. That's true about Gomm and Pottgard. But 14 we also know, as you've pointed in my report, that the 15 incidence of cancer has been increasing steadily over 16 the last decade, and you can see that the projection is 17 that it will become even more common in terms of cancer 18 mortality in the country. 19 So understanding and knowing that is I 20 think an important thing to take into account as a 21 basal understanding of what we're talking about in 22 terms of cancer risk. 23 Q. Are you specifically relying on cancer 24 inc -- cancer -- rephrase.</p>
<p style="text-align: right;">Page 151</p> <p>1 incidence being relevant, and then talked about adding 2 something to that risk level. I think that's what you 3 were saying. What I'm asking is this. 4 If you have an incidence rate of a 5 particular cancer, as you reflected it here, that 6 incidence rate isn't making any judgments as to what's 7 causing that incidence rate; right. 8 MR. INSOGNA: Form. 9 A. I'm not understanding your question. 10 BY MR. SLATER: 11 Q. You gave me incidence rate -- rephrase. 12 The report state some cancer incidence 13 rates; right? 14 A. Yes. 15 Q. In and of itself, the incidence rate of 16 cancer doesn't tell it how it's being caused or what's 17 contributing to the cause of that cancer; right? 18 A. Not in and of itself, but we know -- for 19 example -- let me clarify. 20 We know that these agents became online in 21 2012, and we know what the incidence rates of cancer 22 have been over the last decade, so we can look at 23 incidence rates before and after, and we can analyze to 24 see are there any increases in incidence, which we're</p>	<p style="text-align: right;">Page 153</p> <p>1 Are you relying on any specific cancer 2 incidence rate as a basis for your opinion as to 3 whether or not NDMA and NDEA can cause any increased 4 risk of cancer to humans? 5 A. No. 6 MR. INSOGNA: Object to form. 7 A. No, I'm relying on that for that part of 8 the opinion. 9 BY MR. SLATER: 10 Q. In terms of the lists of risk factors that 11 you provide for these various cancers, did you list 12 nitrosamines as a risk factor for any of them? 13 A. I -- in this section in the background, 14 no, but we talked about it in the -- nitrosamines in 15 the diet section, where that would be pertinent. 16 Q. Do you agree NDMA and NDEA intake is a 17 risk factor for cancer as a general proposition? 18 A. No. 19 Q. Not for any cancer? 20 A. I think -- I think it's been found to be 21 associated in some studies that I think we're going to 22 get to. 23 Q. Bear with me for one second. I'll be 24 right back.</p>

<p style="text-align: right;">Page 154</p> <p>1 Let me just make sure that I'm asking this 2 question clearly. 3 Do you agree or disagree that -- let me 4 rephrase. 5 Do you agree or disagree that nitrosamines 6 are a risk factor for any cancer, yes or no? 7 MR. INSOGNA: Object to form. 8 A. I disagree. 9 MR. SLATER: Chris, do you have handy the 10 article authored by Dr. Catenacci and another author 11 titled "Toward Personalized Treatment of Advanced 12 Biliary Tract Cancers"? If you do, please put that up 13 on the screen as the next exhibit. 14 MR. GEDDIS: I'll -- 15 MR. SLATER: What? 16 MR. GEDDIS: I'll enter it as an exhibit. 17 MR. SLATER: Yeah. Yeah. Sorry. I 18 didn't hear what you said. Yeah. 19 [Exhibit 12 marked for identification.] 20 BY MR. SLATER: 21 Q. Doctor, do you see on the screen -- and 22 actually, I don't know what number we're up to. Let's 23 just for the record say what exhibit number this is, if 24 anyone knows.</p>	<p style="text-align: right;">Page 156</p> <p>1 extrahepatic cholangiocarcinoma." 2 You see that? 3 A. Yes. 4 Q. What is -- well, rephrase. 5 What is the biliary tract? 6 A. Biliary tract is a set of ducts within the 7 liver that excrete bile into the small bowel, and they 8 also in the bile have enzymes and other factors that 9 help with digestion, and it's also a common route of 10 excretion of degradation products and chemicals. 11 Q. Are nitrosamines, including NDMA and NDEA, 12 metabolized in the liver? 13 A. Yes. 14 Q. What does that mean for them to be 15 metabolized in the liver? 16 A. When you have NDMA or others, they -- if 17 we're talking about an oral uptake or endogenous in the 18 gut, they get absorbed and they get transported to the 19 liver as first path to the portal venous system, which 20 all things taken orally do. 21 And based on enzymes that are in the liver 22 cells, they metabolize things, called first-pass 23 metabolism, that in that case would actually -- part of 24 the metabolism pathway would convert the NDMA to an</p>
<p style="text-align: right;">Page 155</p> <p>1 MR. GEDDIS: 12. 2 THE REPORTER: Yeah, Exhibit 12. 3 MR. SLATER: Great. 4 BY MR. SLATER: 5 Q. Doctor, on the screen is Exhibit 12. It's 6 an article titled "Toward Personalized Treatment of 7 Advanced Biliary Tract Cancers," published in a journal 8 called Discovery Medicine in July 2012. 9 Do you see that? 10 Q. You're one of the coauthors of that 11 article; correct? 12 A. Yes, along with my fellow, Dr. Geynisman. 13 MR. SLATER: Chris, could you scroll down 14 a little bit and then blow up a little bit the 15 introduction at the bottom of that page? Just that 16 first paragraph right there, yeah. That's it. 17 Perfect. 18 BY MR. SLATER: 19 Q. This starts out in the introduction 20 stating, "Biliary tract cancers are comprised of four 21 distinct adenocarcinomas: Gallbladder carcinoma; 22 intrahepatic cholangiocarcinoma; hilar 23 cholangiocarcinoma, also known as a Klatskin tumor and 24 further subclassified by the Bismuth criteria; and D,</p>	<p style="text-align: right;">Page 157</p> <p>1 active metabolite, and then would be excreted through 2 the biliary system after a number of chemical processes 3 that make it conducive to being excreted through the 4 bile, through the biliary tract system that we were 5 talking about. 6 Q. Let's go, if we could, to the second page 7 of this article, which is Page 42, the right-hand 8 column. And there's a heading that says "epidemiology 9 and etiology of biliary tract cancers." 10 Do you see that? 11 A. Yes. 12 Q. I'd like to go down towards the bottom of 13 that column and read this, and then we'll read over to 14 the next page. 15 Towards the bottom of that page, six lines 16 up from the bottom of that paragraph in the right 17 column, it says, "Whereas the majority of patients have 18 no identifiable etiology, known risk factors include 19 chronic inflammatory diseases, including" -- and then 20 there's a list of those diseases. 21 Do you see that? 22 A. Yes. 23 Q. And if you continue on the next page -- 24 MR. SLATER: Can you scroll to the top of</p>

<p>Page 158</p> <p>1 the next page, please, Chris? Perfect.</p> <p>2 BY MR. SLATER:</p> <p>3 Q. After that list, it says, "Chemicals such</p> <p>4 as dioxin nitrosamines and asbestos," and then lists</p> <p>5 some medications and then "other general exposures and</p> <p>6 behaviors, including smoking, obesity, and diabetes.</p> <p>7 Many of these presumably lead to a state of chronic</p> <p>8 inflammation, cancer initiation, and progression."</p> <p>9 That's what you wrote in this 2012</p> <p>10 article; correct?</p> <p>11 A. That's what's written there, similar to as</p> <p>12 I pointed out in the gastric paper that I referenced</p> <p>13 here -- that it was mentioned in that particular paper.</p> <p>14 It's the same concept in that it's an association</p> <p>15 that's been reported. I wasn't -- I was just -- we</p> <p>16 were trying to show all of the literature that's</p> <p>17 reported on various associations that have been</p> <p>18 described.</p> <p>19 Q. My question is this. It's more narrow</p> <p>20 than what you stated. Here's my question.</p> <p>21 In this article you published in 2012,</p> <p>22 that is what you stated; correct?</p> <p>23 A. We stated that it was one of many</p> <p>24 associations with this cancer, but without going into</p>	<p>Page 160</p> <p>1 factors; correct?</p> <p>2 MR. INSOGNA: Object to form.</p> <p>3 A. As explained before, but it does say</p> <p>4 nitrosamines as a group.</p> <p>5 BY MR. SLATER:</p> <p>6 Q. Within the group of -- rephrase.</p> <p>7 This states that nitrosamines are known</p> <p>8 risk factors for biliary tract cancers, and that</p> <p>9 includes NDMA and NDEA? They are nitrosamines;</p> <p>10 correct?</p> <p>11 MR. INSOGNA: Object to form. Compound.</p> <p>12 A. Those are one of hundreds, I believe, of</p> <p>13 different nitrosamines. So this is not specific to any</p> <p>14 one. It's an overall review paper noting previously</p> <p>15 reported associations with these cancer.</p> <p>16 BY MR. SLATER:</p> <p>17 Q. As you sit here now, you agree with me</p> <p>18 that nitrosamines, including NDMA and NDEA, are known</p> <p>19 risk factors for biliary tract cancer; correct?</p> <p>20 MR. INSOGNA: Object to form.</p> <p>21 A. As we'll talk about when we get to the</p> <p>22 studies looking at nitrosamines in dietary and other</p> <p>23 studies, there are well-recognized papers, many of</p> <p>24 which we talk about here, that suggest association of</p>
<p>Page 159</p> <p>1 detail, because that wasn't the focus of this paper.</p> <p>2 Q. Well, I don't see the word "association"</p> <p>3 in that paragraph because it doesn't appear in that</p> <p>4 paragraph; correct?</p> <p>5 MR. INSOGNA: Object to form.</p> <p>6 A. That's what's implied.</p> <p>7 BY MR. SLATER:</p> <p>8 Q. Is the answer to my -- my question is</p> <p>9 this. New question.</p> <p>10 The word "association" does not appear</p> <p>11 there; instead you use the word "known risk factors."</p> <p>12 Correct?</p> <p>13 A. That's what is used in that -- the</p> <p>14 terminology that is used there, yes.</p> <p>15 Q. And the specific terminology relative to</p> <p>16 what we're talking about here in this deposition is</p> <p>17 that you in a published article in 2012 said that the</p> <p>18 known risk factors for these biliary tract cancers</p> <p>19 includes chemicals such as nitrosamines; correct?</p> <p>20 A. It does say that. I'm telling you that</p> <p>21 implies that these are what have been associated in the</p> <p>22 literature. I'll point out it doesn't say NDMA or</p> <p>23 NDEA.</p> <p>24 Q. This refers to nitrosamines as known risk</p>	<p>Page 161</p> <p>1 nitrosamines with various cancers.</p> <p>2 BY MR. SLATER:</p> <p>3 Q. In terms --</p> <p>4 A. And there are other --</p> <p>5 Q. In terms of my specific question, you</p> <p>6 agree with me as you sit here right now that</p> <p>7 nitrosamines, including NDMA and NDEA, are known risk</p> <p>8 factors for biliary tract cancers; correct?</p> <p>9 MR. INSOGNA: Object to form. Asked and</p> <p>10 answered.</p> <p>11 A. I'm trying to tell you that what that</p> <p>12 means is that there are known papers that reported</p> <p>13 associations with nitrosamines for various cancers, and</p> <p>14 I pointed one out earlier, including this one, and I</p> <p>15 think we'll talk about it later when we get to the</p> <p>16 dietary papers.</p> <p>17 BY MR. SLATER:</p> <p>18 Q. I'm not asking about where, when, or why.</p> <p>19 I'm just asking this question.</p> <p>20 As you sit here now, you agree with me</p> <p>21 that nitrosamines, including NDMA and NDEA, are known</p> <p>22 risk factors for biliary tract cancers; correct?</p> <p>23 MR. INSOGNA: Object to form. Asked and</p> <p>24 answered.</p>

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1 A. There are known reports that have looked
 2 at that association and various cancers, including
 3 biliary tract cancers.
 4 BY MR. SLATER:
 5 Q. Is the answer to my question yes, that
 6 they are known risk factors?
 7 MR. INSOGNA: Object to form. Asked and
 8 answered.
 9 A. There are known -- there are known papers
 10 that have looked at them as risk factors and reported
 11 associations in both positive and negative studies.
 12 BY MR. SLATER:
 13 Q. Again, I'm not asking about other papers.
 14 I'm not asking about the why or wherefore. It's a very
 15 narrow, very direct question.
 16 Do you agree with me as you sit here now
 17 that nitrosamines, including NDMA and NDEA, are known
 18 risk factors for biliary tract cancer?
 19 MR. INSOGNA: Object to form. That's the
 20 fourth time you've asked the question. He's answered
 21 it.
 22 A. The way you're asking that question, the
 23 answer is no.
 24 BY MR. SLATER:

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1 Q. When you stated in your paper in 2012 that
 2 you published that nitrosamines are known risk factors
 3 for biliary tract cancers, was that a true statement?
 4 MR. INSOGNA: Form.
 5 A. I'm telling you what was meant by that
 6 statement and that there are known associations of
 7 nitrosamines with this cancer that was the topic of
 8 this paper that have been reported.
 9 Whether I agreed with that comment or not,
 10 I was -- as we talked about earlier, I was reporting
 11 what has been reported in other papers as a review
 12 article, not even in detail.
 13 BY MR. SLATER:
 14 Q. Was that a true statement when you made it
 15 in your paper in 2012?
 16 MR. INSOGNA: Object to form. Asked and
 17 answered.
 18 A. As I stated, yes.
 19 BY MR. SLATER:
 20 Q. The answer is yes; correct?
 21 MR. INSOGNA: Object to form. Asked and
 22 answered.
 23 A. As I stated, that is correct.
 24 BY MR. SLATER:

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1 Q. Well, I just wanted it -- honestly would
 2 appreciate just -- it hasn't been asked and answered,
 3 because I don't know what "as I stated" means, I don't
 4 know if that's supposed to bring in all the other
 5 things I didn't ask about, so I would really appreciate
 6 it, Doctor, if you could just answer this question with
 7 a direct yes or no.
 8 When you stated in 2012 in a published
 9 article that nitrosamines are known risk factors for
 10 biliary tract cancer, was that a true statement? Yes
 11 or no?
 12 MR. INSOGNA: Object to form. Asked and
 13 answered. He does not have to answer the question the
 14 way you want him to. The --
 15 A. I can't answer that yes, no, without the
 16 qualification and the explanation I've given a few
 17 times now.
 18 BY MR. SLATER:
 19 Q. Doctor, the explanation can be requested
 20 either by me in a subsequent question or by defense
 21 counsel when they get to question you. I didn't ask
 22 you why it's true, and I didn't ask you why you said
 23 it, but you keep telling me that, so that's -- but
 24 that's not what I'm asking. So I'm going to try this

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1 again with you.
 2 When you stated in a published paper in
 3 2012 that nitrosamines are known risk factors for
 4 biliary tract cancers, was that a true statement? Yes
 5 or no?
 6 MR. INSOGNA: Object to form. Asked and
 7 answered.
 8 A. I answered that as best as I can up until
 9 this point.
 10 BY MR. SLATER:
 11 Q. Was it a true statement? Yes or no?
 12 MR. INSOGNA: Object to form. Asked and
 13 answered.
 14 A. It is true that it was an association that
 15 was recognized in a number of papers that nitrosamines
 16 and all the other things listed there are associated
 17 with this cancer.
 18 BY MR. SLATER:
 19 Q. Yes or no?
 20 MR. INSOGNA: Same objection.
 21 A. What's the question?
 22 BY MR. SLATER:
 23 Q. When you stated in a published paper in
 24 2012 that nitrosamines are known risk factors for

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1 biliary tract cancers, was that a true statement?
 2 MR. INSOGNA: Same objection. Asked and
 3 answered.
 4 A. I can't answer that any other way than I
 5 already have. I can keep giving you the same answer.
 6 BY MR. SLATER:
 7 Q. Well, Doctor, you're an expert witness
 8 here, so this isn't your first time in a deposition,
 9 and you understand that you're supposed to answer the
 10 questions as directly as you can.
 11 If the lawyer who hired you who's sitting
 12 to your side wants to ask you why is that a true
 13 statement and you want to talk about associations and
 14 things, you certainly can do that in a subsequent part
 15 of the deposition, but I'm not asking you the why, and
 16 I'm not asking what it meant. I'm asking as it's
 17 phrased in this published paper.
 18 MR. INSOGNA: Counsel --
 19 BY MR. SLATER:
 20 Q. So I'll try it one more time. Perhaps
 21 with that clarification, we can get past this speed
 22 bump.
 23 When you stated in a published paper in
 24 2012 that nitrosamines are known risk factors for

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1 biliary tract cancers, was that a true statement? Yes
 2 or no?
 3 MR. INSOGNA: Same objection. Asked and
 4 answered. He has just stated he has no other way to
 5 answer this question. You can continue to bully him,
 6 he can continue to give you the answer. You can answer
 7 it again.
 8 A. We all see the statement. I was trying to
 9 make sure that the underlying intention and meaning of
 10 the statement was relayed.
 11 BY MR. SLATER:
 12 Q. If you want to relay the underlying
 13 intention and the meaning of the statement, I'm sure
 14 that you can tell during a break the lawyer who's
 15 sitting to your side, and then he'll ask you the
 16 question later, or maybe I'll follow up with it, but
 17 I'm just trying to go step-by-step. So starting with
 18 the simple, I'll try it one more time.
 19 When you stated in a published paper in
 20 2012 that nitrosamines are known risk factors for
 21 biliary tract cancers, was that a true statement? Yes
 22 or no?
 23 MR. INSOGNA: Same objection. Asked and
 24 answered.

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1 A. The statement is there, and I defined what
 2 it means.
 3 BY MR. SLATER:
 4 Q. The statement that was made in this
 5 paper -- is that a true statement or not?
 6 MR. INSOGNA: Same objection. Asked and
 7 answered.
 8 A. A descriptive statement of available
 9 studies as a review paper.
 10 BY MR. SLATER:
 11 Q. Doctor, is there a reason why you don't
 12 want to just say that what you wrote in a published
 13 paper was true? You keep saying you want to explain
 14 why it's true and what you meant by it, but I'm not
 15 asking you that question. I'm just asking if what you
 16 published was a true statement.
 17 I would really appreciate it if I could
 18 get -- this -- we were asked before how long this is
 19 going to take. We've now hit, "It's not going that
 20 quick." So I'm going to try it one more time.
 21 When you stated in a published paper -- I
 22 don't know why you're looking at your counsel, if you
 23 are looking at counsel. Right?
 24 But you don't need -- let me just say

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1 something. I've been watching this the entire
 2 deposition, in good faith, assuming that Dr. Catenacci
 3 is just waiting for objections. But I don't think that
 4 he needs to look at you every single time he answers a
 5 question, and I don't appreciate it, because I don't
 6 think that's appropriate.
 7 MR. INSOGNA: Adam, there's --
 8 BY MR. SLATER:
 9 Q. So I'm going to try this again.
 10 MR. INSOGNA: Adam, there is an attorney
 11 for your side in the room who can tell you that --
 12 MR. SLATER: I don't care. I'm going to
 13 try to continue this deposition. I'm commenting on the
 14 record that Dr. Catenacci -- and we have a video, it
 15 will speak for itself -- is looking at you almost every
 16 single time I ask a question. Okay? So I'd prefer to
 17 just --
 18 MR. INSOGNA: I have to correct that
 19 colloquy, because it's inaccurate. There are two
 20 screens, one in front of you and one to the doctor's
 21 right where the document is being shown. You have an
 22 attorney for your side present in the room who can tell
 23 you if he's looking at me or if I'm looking at him, and
 24 I am not. I am looking directly at the screen. Okay?

<p style="text-align: right;">Page 170</p> <p>1 You've asked this question probably eight 2 times now. He has given you his answer and told you 3 that's the only way he knows how to answer the 4 question. 5 MR. SLATER: And counsel, I don't want to 6 argue with you, okay, because we can do this if we need 7 to at another time in another venue. 8 BY MR. SLATER: 9 Q. When you stated in a published article in 10 2012 that nitrosamines are known risk factors for 11 biliary tract cancers, was that a true statement? Yes 12 or no? 13 MR. INSOGNA: Same objection. Asked and 14 answered. 15 A. That is the statement that's there, and 16 I've qualified what I meant by it. 17 BY MR. SLATER: 18 Q. Is it a true statement? Yes or no? 19 A. As I answered, it's true. 20 Q. As you sit here right now, it's true that 21 NDMA and NDEA are known risk factors for biliary tract 22 cancers; correct? 23 MR. INSOGNA: Same objection. Asked and 24 answered. Now misstating the document.</p>	<p style="text-align: right;">Page 172</p> <p>1 you under -- 2 Q. Well, I haven't asked you to explain them, 3 though, and you keep trying to explain them, and I 4 don't really understand why. I'm asking you one 5 question, and you're answering one I didn't ask you, 6 and they're very different. 7 So I would appreciate -- if I don't ask 8 for an explanation, there's no need to give me an 9 explanation. 10 A. Is there a question? 11 MR. INSOGNA: There's no question. 12 BY MR. SLATER: 13 Q. There is peer-reviewed literature 14 establishing an association between NDMA and NDEA and 15 human cancers; correct? 16 A. Establishing associations? 17 Q. Yes. 18 A. Yes, I think I referenced some of them and 19 discussed them, that there are papers that have 20 reported associations in various cancers and various 21 assessments. 22 Q. You refer in this section of the report to 23 medical societies and whether they list NDMA as a risk 24 factor for certain cancers; right?</p>
<p style="text-align: right;">Page 171</p> <p>1 MR. SLATER: It's actually a different 2 question. I'll ask it differently. 3 BY MR. SLATER: 4 Q. As you sit here right now, are 5 nitrosamines known risk factors for biliary tract 6 cancers? 7 A. No. 8 Q. They're not known risk factors anymore? 9 That changed since 2012? 10 A. There are associations that have noted 11 nitrosamines through various ways, whether it's 12 occupational, whether it's by diet, that have shown 13 associations with various cancers. There are similar 14 papers that have shown no associations. 15 And so if you're asking me if there's a 16 known risk factor for this, first of all, it's quite 17 vague, because what -- are we talking about how -- what 18 are the exposures, at what levels, et cetera? 19 So as you asked it, the answer is no. 20 Q. Well, I'm using the language you used in 21 your published peer-reviewed article, so I'm not using 22 any language that's foreign to you, because this is 23 your own words; right? 24 A. I'm trying to explain those to you so that</p>	<p style="text-align: right;">Page 173</p> <p>1 A. Yes. 2 Q. You don't list those medical societies -- 3 rephrase. 4 You don't list the actual medical society 5 statements in your list of materials considered; right? 6 A. Right. As I mentioned earlier, when it 7 was something that was common knowledge that I didn't 8 need to reference, just based on these are statements 9 that we do every day in terms of clinical care of our 10 patients. 11 Q. The actual statements that you're 12 referring to are not listed in your list of materials 13 considered nor were they provided to us with your 14 materials considered; right? 15 MR. INSOGNA: Object to form. 16 A. Other than the answer I provided, no, 17 they're not there. 18 BY MR. SLATER: 19 Q. And for example, you didn't provide the 20 dates of those society statements or the methodology 21 that was followed by them coming up with these 22 purported statements; right? That's not discussed in 23 the report; right? 24 MR. INSOGNA: Object to form.</p>

<p style="text-align: right;">Page 174</p> <p>1 A. I didn't put that explicitly in the 2 report, no. 3 BY MR. SLATER: 4 Q. If I understood your -- rephrase. 5 If I understand your thinking, you use the 6 word "risk factor" and "association" essentially 7 interchangeably. Do I understand that? 8 MR. INSOGNA: Object to form. Misstates 9 the testimony. 10 MR. SLATER: Well, I'm not misstating it; 11 I'm asking it. So I don't know why you're objecting, 12 counsel. Are you telling him to disagree with me, 13 or -- I don't understand the objection. What's the 14 objection? 15 MR. INSOGNA: My objection is you've 16 characterized his testimony -- I think you've 17 mischaracterized. He can answer you if he disagrees 18 with me. If he disagrees with you -- I told him he 19 could answer. 20 MR. SLATER: Okay. Well, I didn't 21 characterize it. I actually asked if my 22 characterization was accurate. It's a different 23 question. I have an issue with your objection, because 24 I feel like it can be a suggestion, perhaps, as to how</p>	<p style="text-align: right;">Page 176</p> <p>1 MR. INSOGNA: Object to form. 2 A. Bit of a vague question. Can you be a 3 little bit more detailed which cancer we're talking 4 about? 5 BY MR. SLATER: 6 Q. You went through a whole series of cancers 7 in section -- 8 A. Yes. 9 Q. And my question is this. Because there is 10 literature suggesting an association between NDMA and 11 each of those different cancers, would you agree that 12 there's at least an association thus that those 13 substances are risk factors for those cancers? 14 A. I would say potential risk factors, which 15 in the end I think is another way to characterize that 16 paragraph, would have been potential risk factors. 17 Q. We talked earlier about precision in 18 writing a report or a peer-reviewed article; right? 19 A. Yes, we did. 20 Q. You didn't use the word "potential" in 21 either your article in 2012 or the report; right? 22 A. The report? I didn't talk about 23 nitrosamines in this particular paragraph. 24 Q. You actually did not recognize at all in</p>
<p style="text-align: right;">Page 175</p> <p>1 to answer the question, so I'm just flagging that for 2 the record. 3 MR. INSOGNA: My understanding is that we 4 are allowed to give explanations for our objections, 5 but noted. 6 BY MR. SLATER: 7 Q. Do you equate a risk factor with an 8 association? 9 A. Not always, but in this instance where we 10 were talking about various things that have been 11 associated with cancer and being well-recognized as 12 potential risk factors for cancer, we listed all of the 13 references that were there that have been in the 14 literature. 15 Q. You're talking about your article in 2012? 16 A. And also, similar to the other one, where 17 we were doing a review on gastroesophageal cancer and 18 we were -- mentioned a similar phrase. I think in that 19 actual paper it says associated with, as opposed to a 20 risk factor. 21 Q. With regard to all the cancers that were 22 listed, there is literature suggesting association for 23 each of them, thus you would consider NDMA and NDEA to 24 be risk factors for each of those cancers; correct?</p>	<p style="text-align: right;">Page 177</p> <p>1 your report the fact that nitrosamines are potential 2 risk factors as you now state for these cancers. That 3 was not stated; right? 4 MR. INSOGNA: Object to form. 5 A. That's not true. I talked about them as a 6 whole section later on, and the data for and against 7 it. 8 BY MR. SLATER: 9 Q. Well, I'm talking about in this section, 10 the introduction to cancers summary, where you 11 suggested through your reference to the lack of medical 12 society listings of NDMA as a risk factor, you were 13 suggesting it's not a risk factor; right? 14 A. I'm suggesting that these are all 15 potential -- that are association studies that have 16 shown some degree of association. That makes them 17 potential risk factors. 18 Q. Well, you didn't say, "Even though the 19 medical societies don't list NDMA or NDEA as risk 20 factors, in my opinion they are potential risk factors 21 for these cancers"? 22 That's not stated; correct? 23 MR. INSOGNA: Object to form. 24 A. My opinion is not that NDMA is a risk</p>

<p style="text-align: right;">Page 178</p> <p>1 factor as a blanket statement without qualifying 2 discussion about it. 3 BY MR. SLATER: 4 Q. Well, I said potential risk factor, which 5 was your phrase. 6 It doesn't say that; right? 7 A. Well, I didn't say -- sorry. 8 MR. INSOGNA: Object to form. 9 A. I didn't that about NDMA. I thought we 10 were talking about nitrosamines. 11 BY MR. SLATER: 12 Q. I'm talking about your report and the 13 language you used in your report. I thought that's 14 what we were talking about. 15 A. I thought we were talking about -- 16 MR. INSOGNA: There's no question pending. 17 BY MR. SLATER: 18 Q. Let's go now to Section 9 of your report 19 on Page 29, please. You have a section titled 20 valsartan and valsartan-containing drugs. That's 21 Section 9. And then 9a is background, generic 22 medications incorporating valsartan. 23 Do you see that? 24 A. Yes.</p>	<p style="text-align: right;">Page 180</p> <p>1 have any association with cancer. 2 Q. Let's talk about that for a moment. 3 As of the reporting of this data in this 4 meta-analysis of 2011, you would not expect that there 5 would have been any NDMA or NDEA in valsartan; right? 6 There's no reason to believe there would have been; 7 correct? 8 A. And besides this is -- when the study was 9 done, this was looking at a meta-analysis of studies 10 done even before that. But yes, so the answer is yes, 11 we wouldn't have expected to be any impurities there. 12 Q. So we know that on this meta-analysis 13 conducted by the FDA as of 2011, when we know there was 14 not NDMA or NDEA in valsartan, the study showed there 15 is no increased risk of cancer at all; right? 16 A. That was important, I think, to understand 17 as a background to the question at hand. 18 Q. Now let's look at Section 10 on Page 30, 19 relevant background, VCDs with NDMA or other 20 impurities. 21 Do you see that? 22 A. Yes. 23 Q. You start out talking about in June 2018, 24 ZHP reported that it had detected the presence of a</p>
<p style="text-align: right;">Page 179</p> <p>1 Q. That's just background information about 2 what the medications are supposed to do; right? 3 A. Yes. 4 Q. The presence of NDMA or NDEA in these 5 medications would provide no benefit whatsoever; right? 6 MR. INSOGNA: Object to form. 7 A. They should not provide known benefit that 8 I'm aware of. 9 BY MR. SLATER: 10 Q. Looking now at Page 29, 9b, where you say 11 that VCDs and ARBs are not associated with an increased 12 cancer risk. 13 You start out talking about an FDA 14 meta-analysis that was reported on June 2, 2011; right? 15 A. Yes. 16 Q. You didn't think that we were claiming in 17 this case that valsartan in and of itself without 18 contamination with NDMA or NDEA causes cancer, did you? 19 A. That was not my opinion or the intention 20 of including this section. The intention of including 21 this section is that first of all there were studies 22 analyzing it, and I thought it was pertinent to 23 understand that the drug by itself prior to any of this 24 happening -- this was done on June 2nd, 2011 -- did not</p>	<p style="text-align: right;">Page 181</p> <p>1 previous undetected impurity, NDMA, in the active 2 pharmaceutical ingredient for valsartan; right? 3 A. Yes. 4 Q. Have you been shown any documents 5 indicating that ZHP actually knew that there was NDMA 6 in its valsartan before June 2018? 7 MR. INSOGNA: Object to form. 8 A. Not that I'm aware of. 9 BY MR. SLATER: 10 Q. You would agree with me that -- well, I'll 11 withdraw that. 12 Why did you point out that it was 13 previously undetected? Just because -- well, rephrase. 14 Why did you point out that this was 15 previously undetected? 16 A. I believe I got that from the FDA website 17 where I got this information. In other words, that it 18 was -- there was a time point at which it was not known 19 to be there. 20 Q. Did that -- was that of any significance 21 to you in forming your opinions? 22 A. Not for the questions at hand for me, no. 23 Other than, I mean, when we're talking about the 24 duration of exposure, we'd want to know when it's</p>

<p style="text-align: right;">Page 182</p> <p>1 thought that this was first -- when they first began 2 having these impurities, which I think was determined, 3 and so we know it was in 2012, I believe. 4 So that would be an important thing to 5 understand, because when we look at the epi data, the 6 studies are looking at the time point at which the 7 drugs were available. 8 Q. And then evaluating the epi data, it's 9 important to have a good understanding of which of the 10 subjects in the study took valsartan contaminated with 11 NDMA and which were not taking contaminated NDMA -- 12 contaminated valsartan; correct? 13 A. That would be an important thing to do in 14 that study, which is what was attempted to be done, 15 yes. Both of the studies -- Pottgard and Gomm. 16 Q. In fact, the structure of the study relies 17 heavily on assumptions as to which people were exposed 18 to contaminated valsartan and which were not; right? 19 MR. INSOGNA: Object to form. 20 A. Attempts were made to identify which lots 21 were involved and which ones weren't, and they defined 22 them as definitely not, probably, and possibly. And 23 they looked at it through different sensitivity 24 analyses, excluding the possibly, just the probably, to</p>	<p style="text-align: right;">Page 184</p> <p>1 You quoted that there; right? 2 A. Yes. 3 Q. The understanding was you're taking 4 valsartan due to hypertension and to prevent 5 significant cardiovascular injury versus the risk of 6 using the drug for a short period of time further and 7 entertaining a potential risk of cancer? 8 That's basically what was being weighed; 9 right? 10 A. Right. It was weighing risks and benefits 11 of things, and I think that's why I pointed it out, 12 that it was felt that the risk of stopping the drug was 13 worse than continuing the drug until replacements could 14 be found. 15 And later down I think I pointed out that 16 the risk -- the actual risk of not taking valsartan for 17 hypertension is actually really minimal, so sort of 18 shows you how minuscule the risk was of continued 19 impurity in the VCDs. 20 I think that's on page -- I'd have to look 21 and see exactly which page to point you to that, but 22 it's in there. So -- 23 Q. The FDA in statements consistently told 24 patients to make sure they spoke to their doctor and</p>
<p style="text-align: right;">Page 183</p> <p>1 make sure that the conclusions were consistent. 2 BY MR. SLATER: 3 Q. Well, to the extent -- 4 A. That was what was available. That's the 5 best evidence that was available to them. 6 Q. If that -- rephrase. 7 If those assumptions were wrong, that 8 could impact the data and the significance of the data; 9 right? 10 MR. INSOGNA: Object to form. 11 A. They -- the answer to your question is 12 that if assumptions are wrong in a study, they can 13 affect and influence the outcome of the data, as in any 14 study. And those assumptions I think, in my opinion, 15 after reviewing the papers and what they did to 16 identify those, is really the highest quality evidence 17 that we have to look at this question to date. 18 BY MR. SLATER: 19 Q. We'll come back to that; I promise. 20 Looking at your report, Page 30 to 31, you 21 quoted some FDA statements, including the statement 22 that, "Patients taking the recalled 23 valsartan-containing medicines should continue taking 24 their medicine until they have a replacement product."</p>	<p style="text-align: right;">Page 185</p> <p>1 secured a replacement medication before ceasing their 2 valsartan; right? 3 MR. INSOGNA: Object to form. 4 A. Can you repeat that again? I missed the 5 beginning of the question. 6 BY MR. SLATER: 7 Q. What we just read states that patients 8 should speak to their doctor, continue taking the 9 valsartan until they have a replacement product. 10 That's what the FDA told people; right? 11 A. Yes, that's what we just talked about. In 12 other words, the risk of stopping it was larger than 13 taking it if it had an impurity in it. That's how I 14 see that. 15 Q. Right. The risk of stopping it 16 encompassed the risk of having, for example, a heart 17 attack the next day; right? 18 That's one of the risks; right? 19 A. That's one of the risks, and that's why I 20 was pointing you to Page 33 at the top. The actual 21 risk is actually small in stopping the drug, but it's 22 better -- they're standard treatments to take for these 23 conditions because they improve outcomes, but the 24 actual improvement is actually marginal.</p>

<p style="text-align: right;">Page 186</p> <p>1 And despite that, they still were told to</p> <p>2 stay on it instead of stop them, which tells me that</p> <p>3 the calculated risk of continuing the drug was low</p> <p>4 compared to stopping it.</p> <p>5 Q. Where are you saying that the FDA said</p> <p>6 taking the medication act -- rephrase.</p> <p>7 Where are you pointing to where it says</p> <p>8 stopping the medication actually doesn't create any</p> <p>9 risk or creates very little risk?</p> <p>10 A. Reask -- say that again. Clarify the</p> <p>11 question.</p> <p>12 Q. I thought what you just told me is that</p> <p>13 the FDA later came out and said that the risk of</p> <p>14 stopping your valsartan and having any sort of an</p> <p>15 adverse event as a result of stopping your hypertension</p> <p>16 medication is very, very small.</p> <p>17 Did I misunderstand what you said?</p> <p>18 A. You misunderstand what I said. If you go</p> <p>19 to Page 33, this is now my interpretation of what</p> <p>20 statement that FDA said was, is that when you look at</p> <p>21 the actual risk reduction of adverse events that</p> <p>22 hyper -- that valsartan and other blood pressure</p> <p>23 medications mitigate, they do improve outcomes, but</p> <p>24 they're not dramatic improvements.</p>	<p style="text-align: right;">Page 188</p> <p>1 taking these drugs was higher than the risk of</p> <p>2 continuing -- and stopping the valsartan drugs, then</p> <p>3 they would have said stop the drug, because the risk of</p> <p>4 stopping was not as high as continually taking them.</p> <p>5 Does that make sense to you?</p> <p>6 Q. Well --</p> <p>7 A. So they were saying the risk that we</p> <p>8 calculated is very low, as I quoted several times, and</p> <p>9 that it's better to stay on the drug, because that's</p> <p>10 more of a risk to stop it.</p> <p>11 And I'm telling you when you calculate</p> <p>12 that risk of stopping it, it would be very small, which</p> <p>13 tells you that the risk of continuing the</p> <p>14 valsartan-containing drugs with impurity is even</p> <p>15 smaller than that. That's all I'm saying.</p> <p>16 Q. All right, but in the real world, what the</p> <p>17 FDA was telling people is, "We don't want you to get</p> <p>18 off the drug for days or weeks while you look for a new</p> <p>19 replacement drug"?</p> <p>20 That's what they told people; right?</p> <p>21 A. Because it was felt that it was not that</p> <p>22 much of a risk to stay on it. To stay on the drugs, it</p> <p>23 wasn't that much of a risk. If it was deemed to be a</p> <p>24 higher risk, they would have said stop the drugs, it's</p>
<p style="text-align: right;">Page 187</p> <p>1 In other words, if you were to stop it, it</p> <p>2 wouldn't be -- there was no survival differ -- all</p> <p>3 causes of death did not show any differences between</p> <p>4 these groups. So in other words, stopping it wouldn't</p> <p>5 have had that much of a detriment.</p> <p>6 But despite this knowledge and knowing</p> <p>7 about these drugs, the FDA adjudicated that it was</p> <p>8 still worth staying on the drug because the risk of</p> <p>9 taking the valsartan-containing impurities was even</p> <p>10 lower than that. That's my point.</p> <p>11 Q. So you think the FDA told people to keep</p> <p>12 taking their valsartan so they wouldn't have, for</p> <p>13 example, a heart attack or a stroke or some adverse</p> <p>14 cardiovascular event, and that the FDA thought that was</p> <p>15 a minuscule risk and told people to keep taking the</p> <p>16 drug anyway?</p> <p>17 MR. INSOGNA: Object to form. You may --</p> <p>18 BY MR. SLATER:</p> <p>19 Q. Is that your testimony, Doctor? Like does</p> <p>20 anybody agree with you in the world about that that you</p> <p>21 know of?</p> <p>22 A. Let me answer it in a different way so you</p> <p>23 understand what I'm saying.</p> <p>24 If it was calculated that the risk of</p>	<p style="text-align: right;">Page 189</p> <p>1 worth stopping them, and accepting the risk of not</p> <p>2 getting the benefit from the blood pressure medicine.</p> <p>3 Q. What they said is the risk of stopping the</p> <p>4 blood pressure drug, which could kill you in a couple</p> <p>5 of days potentially, was considered to be a worse</p> <p>6 choice than continuing to take the pills for a few more</p> <p>7 days or even a few weeks, which could potentially cause</p> <p>8 cancer down the line?</p> <p>9 That was the trade-off; right?</p> <p>10 MR. INSOGNA: Object to form.</p> <p>11 BY MR. SLATER:</p> <p>12 Q. That's the trade-off the FDA was</p> <p>13 providing; right?</p> <p>14 A. The FDA was calculating what the risks</p> <p>15 were of staying on the drugs or not staying on the</p> <p>16 drugs, and the consequences of each approach. And they</p> <p>17 obviously stated that they thought the risks of staying</p> <p>18 on it were minimal, and to stay on the drug, because</p> <p>19 the risks of stopping it was higher from getting a</p> <p>20 cardiac or other complication.</p> <p>21 And what I'm telling you is those actual</p> <p>22 risks are low when you look at the data in that</p> <p>23 paragraph on top of Page 33. That's why I included</p> <p>24 that there.</p>

<p style="text-align: right;">Page 190</p> <p>1 In a different scenario, different</p> <p>2 hypothetical scenario, if the risk of a drug became</p> <p>3 higher of continually taking it than actually just</p> <p>4 stopping it, then they would have said that instead.</p> <p>5 That's my point.</p> <p>6 Q. This was the risk of getting off the drug</p> <p>7 for a couple of days, because they only wanted people</p> <p>8 to stay on the drug for a very short time until they</p> <p>9 could get a replacement?</p> <p>10 That's what the FDA said; right?</p> <p>11 MR. INSOGNA: Object to form.</p> <p>12 BY MR. SLATER:</p> <p>13 Q. Is that what the FDA said, Doctor?</p> <p>14 A. It stated here -- and I think we agree on</p> <p>15 that, and what I'm trying to tell you is the</p> <p>16 interpretation is that the risk was considered very</p> <p>17 minimal, which I think is verbatim from what they've</p> <p>18 said, is that the actual risk is very low.</p> <p>19 Q. Did the FDA -- did the FDA say, "Well, go</p> <p>20 ahead and stay on the valsartan with the contamination</p> <p>21 with NDMA and NDEA for the rest of your life. Go</p> <p>22 ahead. No problem"?</p> <p>23 Did the FDA ever say that?</p> <p>24 A. No, they did not say that.</p>	<p style="text-align: right;">Page 192</p> <p>1 recommend the uncontaminated pills that don't have NDMA</p> <p>2 or NDEA; correct?</p> <p>3 MR. INSOGNA: Object to form.</p> <p>4 A. That's a different question, and I would</p> <p>5 agree with that. If I had a choice, I would choose the</p> <p>6 one that doesn't have it. You were asking and we were</p> <p>7 talking about weighing the risks of taking it versus</p> <p>8 stopping the drug, and that's a different question.</p> <p>9 And the risk of stopping it was deemed higher than the</p> <p>10 risk of continuing it.</p> <p>11 And what I'm telling you is that the risk</p> <p>12 of stopping it was a minuscule risk to begin with from</p> <p>13 the data that I quoted here, and that implicitly that</p> <p>14 means the risk was lower than -- in terms of just</p> <p>15 continuing it. It was a minuscule risk, and I think</p> <p>16 the FDA even stated it was a low risk for patients.</p> <p>17 MR. SLATER: Just for the record -- and I</p> <p>18 want to just tell the counsel this just so I preserve</p> <p>19 my rights. I'm not moving to strike any of the</p> <p>20 questions during this deposition, because I was</p> <p>21 instructed not to, and that my rights are still</p> <p>22 preserved, so I don't want my lack of motions to strike</p> <p>23 to be interpreted by anybody as me not -- or be</p> <p>24 interpreted as me thinking that all these answers are</p>
<p style="text-align: right;">Page 191</p> <p>1 Q. What the FDA did was address a potential</p> <p>2 drug shortage because of how widespread the</p> <p>3 contamination was, address the risk of getting off your</p> <p>4 hypertension medication for a few days?</p> <p>5 That's what the FDA was looking at; right?</p> <p>6 MR. INSOGNA: Object to form.</p> <p>7 A. I think it was more than a few days. It</p> <p>8 was a few months that they were anticipating them to be</p> <p>9 on the drugs. And I think, as I said many times, they</p> <p>10 calculated what they thought the risks would be of</p> <p>11 staying on these drugs with impurities versus not, and</p> <p>12 the calculation was stay on them.</p> <p>13 And what I'm telling you is that the</p> <p>14 consequence of stopping the drugs was actually</p> <p>15 considered quite small anyway, so that tells you that</p> <p>16 the risk of staying on them was quite minuscule.</p> <p>17 BY MR. SLATER:</p> <p>18 Q. Would you agree with me that it would be</p> <p>19 completely -- well, rephrase.</p> <p>20 If a physician prescribing a blood</p> <p>21 pressure medication to a patient had a choice between</p> <p>22 valsartan-contaminated as these pills were and an</p> <p>23 alternative medication that wasn't contaminated with</p> <p>24 NDMA or NDEA, 10 out of 10 times the doctor would</p>	<p style="text-align: right;">Page 193</p> <p>1 responsive.</p> <p>2 I just want to place it on the record in</p> <p>3 case I have to -- in case I need that bookmarked for</p> <p>4 later.</p> <p>5 BY MR. SLATER:</p> <p>6 Q. There is no physician you can -- well,</p> <p>7 rephrase.</p> <p>8 It would never be reasonable for a</p> <p>9 physician to recommend to a patient the contaminated</p> <p>10 valsartan pills that are at issue in this case versus</p> <p>11 comparable medication that's not contaminated with NDMA</p> <p>12 and NDEA?</p> <p>13 You agree with that; right?</p> <p>14 MR. INSOGNA: Object to form.</p> <p>15 A. What is the question? Whether or not I</p> <p>16 would say to take the pills with or without? Is that</p> <p>17 what you're asking me?</p> <p>18 BY MR. SLATER:</p> <p>19 Q. There is no physician in your opinion who</p> <p>20 could reasonably recommend to a patient to take the</p> <p>21 valsartan with the contamination versus a comparable</p> <p>22 drug with comparable efficacy without the</p> <p>23 contamination; correct?</p> <p>24 A. I think you asked that already, and I</p>

<p style="text-align: right;">Page 194</p> <p>1 agreed, yes, that's true. That was different than the 2 other questions you were asking me. 3 Q. And that's because there's, as you call -- 4 rephrase. 5 And that's because why would anybody 6 entertain this risk if you don't need to; right? 7 MR. INSOGNA: Object to form. 8 A. If you had a choice to not take it, then I 9 agree with you, there would be no reason to do that. 10 BY MR. SLATER: 11 Q. There's no reason -- there's no reason to 12 entertain that risk, right, if you don't have to? 13 MR. INSOGNA: Object to form. 14 A. There's no reason to take the drugs with 15 impurity of NDMA or others because we already 16 acknowledge there's no known benefit to it, so there 17 would be no reason to do that. 18 BY MR. SLATER: 19 Q. Looking at page -- sorry, one second. 20 Looking at Page 30, the first paragraph 21 under Section 10. You indicate, "According to tests of 22 a random selection of API batches performed by ZHP, the 23 levels of NDMA ranged from 3.4 parts per million to 120 24 parts per million, with an average of 66.5 parts per</p>	<p style="text-align: right;">Page 196</p> <p>1 Q. In terms of internal corporate documents 2 showing their testing, and in terms of the documents 3 that we went through in discovery, you're only aware of 4 those that were provided to you by counsel? 5 We already went through that; right? 6 A. Yes. 7 Q. And if you go to Page 34 and 35. You have 8 a table -- it actually is 33 to 35. 9 You have a table of various test results, 10 and that you got from the FDA; right? The FDA's 11 information? 12 A. Yes. 13 Q. Did you get that independently, or was 14 that provided to you? 15 A. I found that online independently. 16 Q. Did you ever ask counsel if these values 17 were consistent with what we learned in discovery when 18 we took depositions of corporate witnesses? 19 MR. INSOGNA: Object to form. Same 20 instruction not to answer anything concerning what you 21 discussed with attorneys. 22 BY MR. SLATER: 23 Q. Did you wonder if those levels were 24 accurate or whether or not higher levels were</p>
<p style="text-align: right;">Page 195</p> <p>1 million." 2 And you reference 214 as the source of 3 that information; correct? 4 A. Yes. 5 Q. And that's a document that was provided to 6 you by counsel listing some NDMA levels; correct? 7 A. Yes. 8 Q. Did counsel ever inform you that there 9 were other documents produced in this litigation that 10 showed ZHP's valsartan was contaminated in some lots 11 with higher levels than what you quoted in your report? 12 MR. INSOGNA: Object to form. I'm going 13 to instruct you not to answer anything about what you 14 discussed with counsel. 15 BY MR. SLATER: 16 Q. I -- well, let me ask it differently. 17 Were you provided any documents by counsel 18 indicating higher levels of contamination with NDMA in 19 ZHP's valsartan? 20 Were you aware of such documents? 21 A. I don't know. I looked at that document 22 and also I looked at obviously the ones online that 23 showed the values that were found in various lots and 24 the ranges for both NDMA and NDEA.</p>	<p style="text-align: right;">Page 197</p> <p>1 potentially disclosed in discovery when we took 2 depositions of witnesses? 3 MR. INSOGNA: Object to form. 4 A. I took the values that the FDA had as the 5 public values and the ones provided here in that one 6 reference in 214. I didn't think otherwise. 7 BY MR. SLATER: 8 Q. If there -- rephrase. 9 If the lawyers who hired you had data and 10 documents from the manufacturers that reflected higher 11 levels of NDMA and NDEA, you would have wanted to be 12 provided those; correct? 13 MR. INSOGNA: Object to form. 14 A. Yes, I would like -- I think as we 15 discussed earlier, I'd like to be able to look at all 16 of the data to weigh in to see what is and isn't 17 relevant and what is important. 18 BY MR. SLATER: 19 Q. Go -- rephrase. 20 Looking a little bit below where we just 21 were talking at the end of the chart at Page 35. You 22 discuss an April 4, 2019, FDA statement. 23 Do you see that? 24 A. Yes.</p>

<p style="text-align: right;">Page 198</p> <p>1 Q. The first paragraph of that statement you 2 quote -- indicates, "While we've concluded through our 3 risk assessments that the maximum possible exposure to 4 nitrosamines, which are also known environmental 5 contaminants and found in water and foods, including 6 meats, dairy products, and vegetables, in ARB medicines 7 appears to be small, their presence in drug products is 8 not acceptable." 9 You agree that the presence of NDMA or 10 NDEA in drug products is not acceptable; right? 11 MR. INSOGNA: Form. 12 A. I wouldn't intentionally put that there. 13 BY MR. SLATER: 14 Q. From your perspective and in your opinion, 15 it would never be acceptable to include NDMA or NDEA in 16 the valsartan pills as we saw in this case; right? 17 MR. INSOGNA: Object to form. 18 A. I would answer it the same as before. I 19 wouldn't put it there intentionally. It doesn't seem 20 to have any benefit. 21 BY MR. SLATER: 22 Q. And it has risk; right? 23 MR. INSOGNA: Object to form. 24 A. Well, I think we'll get to that when we</p>	<p style="text-align: right;">Page 200</p> <p>1 A. Yes. 2 Q. So the FDA defined what it was speaking 3 about as a low risk as being the low risk associated 4 with continuing the medicine until the patient's doctor 5 or pharmacist provides a safe replacement or a 6 different treatment option. 7 That's how the low risk was defined; 8 correct? 9 A. The risk was, as we talked about earlier, 10 they were comparing risks of different things, and 11 their statement there suggests that they felt that the 12 risk of continuing the drugs is low, and that they 13 should stay on the medication until a replacement could 14 be found. 15 Q. They defined the low risk as the risk of 16 continuing the medicine until the patient's doctor or 17 pharmacist provides a safer placement or a different 18 treatment option. 19 That's what the words state; correct? 20 A. Yes. 21 Q. At no point did the FDA say there's no 22 risk from taking these pills; right? 23 A. No. 24 Q. It's not your -- rephrase.</p>
<p style="text-align: right;">Page 199</p> <p>1 talk about my assessment of the literature that's 2 available with respect to NDMA and other nitrosamines, 3 in terms of what the risk is and what models that have 4 been shown at what dose levels and for what duration. 5 BY MR. SLATER: 6 Q. At the outset when these pills were being 7 sold and nobody knew the contamination was there, the 8 patients were intended to take these pills for the rest 9 of their life, likely; right? 10 MR. INSOGNA: Form. 11 A. Very often patients on blood pressure 12 medicines are on those medications for longer periods 13 of time. 14 BY MR. SLATER: 15 Q. If we look further down in that FDA 16 statement, which carries over to Page 36. 17 This actually says in part, "The risk 18 associated with abruptly discontinuing the use of these 19 important medicines far outweighs the low risk that our 20 scientists estimate to be associated with continuing 21 the medicine until the patient's doctor or pharmacist 22 provides a safer placement or a different treatment 23 option." 24 Do you see that?</p>	<p style="text-align: right;">Page 201</p> <p>1 And certainly it's not your opinion 2 there's no risk of taking these pills, right, on a 3 prospective basis? 4 You're not saying there was no risk, 5 you're quantifying the risk; right? 6 A. Yeah, quantifying the risk, and first 7 started with their worst-case scenario risk, which is 8 just on that same page a little lower down, where they 9 make a lot of assumptions, which are all conservative 10 assumptions, to say if patients were taking the highest 11 levels found the whole time that this was the estimated 12 risk to getting cancer over the period of time that 13 they were taking it for the full time. 14 And so as you pointed -- as you asked me, 15 the FDA did not say that there was zero risk, but they 16 were showing that the risks were quite small even in 17 the worst-case scenario. 18 MR. SLATER: Counsel, I think this is 19 probably a good break point. 20 MR. INSOGNA: Okay. We can go off the 21 record and talk about it. 22 MR. SLATER: Off the record. 23 THE VIDEOGRAPHER: We are going off the 24 record -- I'm sorry. We're going off the record at</p>

<p style="text-align: right;">Page 202</p> <p>1 2:50. 2 [A brief recess was taken.] 3 THE VIDEOGRAPHER: We're back on record at 4 3:06 PM. 5 BY MR. SLATER: 6 Q. Looking now at the bottom of Page 37 into 7 38. You referred to a table published on August 20, 8 2018, in an FDA communication. 9 Do you see that? 10 A. Yes. 11 Q. And you actually give some of the ranges 12 of NDMA in certain foods; correct? 13 A. Yes. 14 [Discussion off the record.] 15 BY MR. SLATER: 16 Q. You list the NDMA levels per this table 17 that's referenced for some food; correct? 18 A. Yes. 19 Q. Let's look at that. Cured meat. The 20 figures are in micrograms. 21 Do you see that? 22 A. Yes, I do. 23 Q. If you want to convert that to nanograms, 24 you would multiple by 1,000; right?</p>	<p style="text-align: right;">Page 204</p> <p>1 valsartan pills of NDMA -- rephrase. 2 In terms of the levels of NDMA seen in the 3 valsartan pills, starting with ZHP's manufactured 4 valsartan, the levels are far higher in nanograms than 5 what we see here for food; correct? 6 A. These are referenced levels that were in 7 the FDA table, and I think when we get into the dietary 8 studies, we'll see that many of the estimates are much, 9 much higher than that. 10 So putting that into context, your 11 question about these particular numbers and the ones in 12 this table, the ones in this table are -- range 13 between -- or the table above, that's saying what's the 14 acceptable limit per day is 96 nanograms per day of 15 NDMA. The same page. 16 Q. I'll try it again. 17 The levels of NDMA in these foods, as 18 quoted in your report, are far lower than, for example, 19 the levels seen in the valsartan manufactured by ZHP; 20 correct? 21 A. Some are lower, yes. Some of the ones 22 that were found that were tested didn't have any 23 identified in the lot. Yeah, some were higher. 24 Q. We'll try it again.</p>
<p style="text-align: right;">Page 203</p> <p>1 A. Yes. 2 Q. So for example, for cured meat, in terms 3 of nanograms it would be four to 230 nanograms; right? 4 A. Yes. 5 Q. With smoked meat, it would be four to 6 1,020 nanograms; right? 7 A. Yes. 8 MR. SLATER: Let's go off for a second, 9 please. Can we please go off the record for a second, 10 please? 11 THE REPORTER: Yeah. Michael? 12 THE VIDEOGRAPHER: We're going off the 13 record at 3:08. 14 [Discussion off the record.] 15 THE VIDEOGRAPHER: We're back on the 16 record at 3:09. 17 BY MR. SLATER: 18 Q. For grilled meat, it would be six to 130 19 nanograms; right? 20 A. Yes. 21 Q. For bacon, it would be 70 to 90 nanograms; 22 right? 23 A. Yes. 24 Q. In terms of the levels seen in the</p>	<p style="text-align: right;">Page 205</p> <p>1 These levels of NDMA that you put into 2 your report are far lower than the results of NDMA for 3 the ZHP-manufactured valsartan; correct? 4 A. I think I answered and said that some are 5 lower and some are higher, based on which lot and which 6 pill, and that also these are not my -- this was quoted 7 from the FDA website. This is what was put online. 8 In my report, I talk more extensively 9 about diet and dietary studies, and trying to estimate 10 various levels of NDMA, et cetera, and the limitations 11 of doing that. 12 Q. Doctor, you put these figures in your 13 report deliberately to help support your opinions, 14 because you say right afterwards, "This table makes 15 clear that NDMA exposure is a routine part of human 16 life." 17 Right? 18 A. That was -- 19 MR. INSOGNA: Object to form. 20 A. That was the point, was to show that we 21 are exposed, as the FDA pointed out with some examples 22 from one reference, of what we are exposed to just from 23 a few different meats, for example. 24 This is not an exhaustive list of all the</p>

<p style="text-align: right;">Page 206</p> <p>1 baseline exposure. The point was is that we are 2 inundated with exogenous exposure to NDMA and other 3 things like that on a daily basis. That was the point 4 there. 5 BY MR. SLATER: 6 Q. So the point wasn't what you said in the 7 report where you said, "This table makes clear that 8 NDMA exposure is a routine part of human life. Indeed, 9 as set forth below, estimates for total NDMA 10 consumption often exceed the FDA's suggested acceptable 11 intake"? 12 MR. INSOGNA: Objection. 13 BY MR. SLATER: 14 Q. That's what your report says is the reason 15 why you put that -- those figures there. 16 Is that not true? 17 A. Exactly what I just said to you. I 18 said -- the first sentence is that we are exposed to 19 this routinely, and the second sentence as stated forth 20 below in my report, when we talk about dietary exposure 21 and other exposures, are routine and high -- much 22 higher than the FDA's limit, which I also point out on 23 the same page is 96 nanograms per day. 24 So I think we're agreeing.</p>	<p style="text-align: right;">Page 208</p> <p>1 A. Some of those papers are older, yes. Some 2 are from this decade that are referenced. 3 Q. Did you make any effort to distinguish 4 from study to study whether the dietary NDMA levels 5 stated need to account for efforts by industry to 6 remove nitrates and NDMA from foods? 7 A. I think as we get through it, there are a 8 lot of limitations to these dietary studies in terms of 9 trying to estimate. So -- I didn't hear if you said 10 something. 11 Q. I told my dog to relax. 12 MR. INSOGNA: Continue your answer -- 13 A. No, I lost -- 14 BY MR. SLATER: 15 Q. I was muted so I didn't say it to you. I 16 was on mute. 17 A. I was saying that there are many 18 limitations to these dietary studies in terms of trying 19 to come out with something that's robust. They have so 20 many problems, they're very problematic in terms of 21 looking at the question that I was asked to answer, 22 which is do these levels in these pills increase the 23 risk over what we're exposed to on a routine basis? 24 And so I think, as you saw in my report, I</p>
<p style="text-align: right;">Page 207</p> <p>1 Q. In looking at the tables of the 2 contamination levels that you put in your report, we 3 had gone through earlier where it said -- we have 4 Princeton Pharmaceutical, for example, which was ZHP, 5 for the 320-milligram valsartan pills, in nanograms the 6 NDMA level was 15,180 nanograms to 16,300 nanograms; 7 right? 8 A. Yes, because those are in micrograms in 9 the table, in that table on Page 35. 10 Q. The point I'm making is when we make them 11 equivalent in terms of the measurement of nanograms, 12 the levels of NDMA are massive compared to the levels 13 in the foods as stated in your report; right? 14 MR. INSOGNA: Object to form. 15 A. No, I think I was qualifying that those 16 foods were some examples that were pointed out by the 17 FDA, but I've also in my same report lower down shown 18 the wide range which is extremely higher than that on 19 routine exposure through diet. 20 BY MR. SLATER: 21 Q. And many of the dietary studies that you 22 talk about were performed at a time period before 23 efforts were made to remove nitrates and NDMA from 24 foods; right?</p>	<p style="text-align: right;">Page 209</p> <p>1 conclude that there are many dietary studies of which I 2 discussed that are limited in their ability to help us 3 with that question. 4 And so overall, I think the general 5 opinion and takeaway from the dietary studies to me is 6 that the overall exposure exogenously is much lower 7 than endogenous production, orders of magnitude 8 smaller, and that even looking at just the dietary 9 studies alone, they're very problematic in terms of 10 this particular question, looking at NDMA as opposed to 11 they're looking at nitrosamines, nitrates, nitrates, 12 which is not the same thing, obviously. 13 And so they're looking at surrogates of 14 the question. And then to quantify how much people are 15 taking, they're using questionnaires, which are 16 notoriously limited in so many ways in being 17 quantitative how much is actually going in, and so it's 18 a surrogate of the reality. 19 And so you have to look at the data, which 20 I did, but when I put it together and look at all the 21 pieces of evidence in front of me in terms of the 22 question I was asked, that is not a large component, or 23 I don't put as much emphasis or weight on it as opposed 24 to the human epi studies that have this exact same</p>

<p style="text-align: right;">Page 210</p> <p>1 question being assessed, which is patients taking 2 valsartan with or without the impurity, which is a much 3 more relevant question and more to point. 4 So yes, did I look at all the data? Yes. 5 Did I assess the daily intake of diet in terms of a 6 potential exposure to NDMA? Yes. And I explained to 7 you how that relates to overall how I applied this to 8 the question. 9 But ultimately when I look at the full 10 dataset in totality, this is not as important to me as 11 the human epi studies, which are in humans and looking 12 at what they were exposed to, which is a question that 13 I was asked to do. 14 So that's how I would answer the question 15 about diet and the values that are here and comparing 16 it to what's in the pills. 17 Q. Let's look on Page 38, Section 11, where 18 you talk about the epidemiologic data. 19 Do you see that? 20 A. Yes. 21 Q. You state, "As set forth above, I have 22 been asked to opine on whether there is sufficient data 23 to support the conclusion advanced by some of the 24 plaintiffs' experts in this litigation that, to a</p>	<p style="text-align: right;">Page 212</p> <p>1 Q. And if I understand your methodology in 2 terms of what you relied on -- we'll go through it in 3 more detail step-by-step. 4 It's my understanding that you place the 5 epi studies, the Pottgard and Gomm studies for people 6 who are actually taking valsartan, at the top of what 7 you -- your hierarchy of what you looked at here; 8 correct? 9 A. Of all the available data, that is, yes, 10 the top data, the most relevant data to the question 11 that we're asking. 12 Q. You refer in the next paragraph, the third 13 paragraph under Section 11, to less valuable dietary 14 studies and animal studies, which you say are only 15 weakly related to the inquiry at issue; right? 16 A. Yes. 17 Q. And again, that inquiry is what you 18 referred to just above in terms of the question that 19 you were looking at; right? 20 A. Yes, whether or not the impurities found 21 in valsartan-containing drugs posed any increased risk. 22 Q. For the cancers alleged by the plaintiffs 23 who claim that they have cancer in this case? 24 A. Yes.</p>
<p style="text-align: right;">Page 211</p> <p>1 reasonable degree of medical certainty, ingestion of 2 NDMA at the trace levels detected in some valsartan 3 drugs could have caused the cancers that the plaintiffs 4 have alleged in this litigation." 5 I want to stop there. That's your summary 6 of what the ultimate question was that you were 7 evaluating; correct? 8 MR. INSOGNA: Form. 9 A. This was one of the questions that I was 10 asked, yes. 11 BY MR. SLATER: 12 Q. When you refer to the cancers that the 13 plaintiffs have alleged, are you talking about the 14 plaintiffs who have been diagnosed with cancer who were 15 saying that cancer was caused or contributed to by 16 their intake of the contaminated valsartan? 17 A. Yes, it's the list of the cancers that 18 were provided to me that have been included in this 19 case. 20 Q. You state in the second paragraph that you 21 placed the most weight on the epidemiologic data that 22 actually studies the relationship between the exposure 23 and the effect; right? 24 A. Yes, the human epidemiological data.</p>	<p style="text-align: right;">Page 213</p> <p>1 Q. So let's start to walk through this a 2 little bit. You talk -- rephrase. 3 Let's look at Section 11a. And you talk 4 about the fact that there's two large cohort studies of 5 people who fill prescriptions for valsartan produced by 6 manufacturers in which the NDMA impurity was 7 identified. 8 And again, that's the Pottgard and Gomm 9 studies; correct? 10 A. Yes. 11 Q. Now, you say those studies compared 12 individuals who took valsartan known or presumed to 13 contain the NDMA impurity and individuals who took 14 valsartan not believed to contain the impurity; right? 15 A. Yes, that was the general methodology of 16 the study. 17 Q. Would you agree with me that there is 18 uncertainty as to whether or not those assumptions are 19 actually met as to all the study participants? 20 MR. INSOGNA: Object to form. 21 A. There's uncertainty with any assumption in 22 any study, but I think it's a reasonable assumption 23 that based on their tracking method in those national 24 databases looking at the prescription level and</p>

<p style="text-align: right;">Page 214</p> <p>1 actually filling scripts -- I mean, they went through 2 every step possible to minimize any error in that 3 assumption. 4 BY MR. SLATER: 5 Q. Do you have the Pottegard study handy? 6 MR. INSOGNA: We can get it. Give us one 7 moment, Adam. 8 MR. SLATER: Chris, you could mark the 9 Pottegard study and just put it in, but I don't need to 10 put it on the screen if the doctor has it. 11 MR. INSOGNA: What did you say? 12 A. 224. That's the reference in my paper. 13 Okay, I have it now in front of me. 14 BY MR. SLATER: 15 Q. Let's look now at the bottom of Page 38 16 where you talk about the Pottegard study. 17 A. Okay. 18 Q. You state that the study subjects were 19 identified from the national Danish registry between 20 September 2011 and June 2017; correct? 21 A. Yes. 22 Q. During that time period, was valsartan 23 sold in this -- to these people who were being studied 24 contaminated with NDMA and/or NDEA for that entire time</p>	<p style="text-align: right;">Page 216</p> <p>1 would be contributing follow-up time to the control 2 arm, the control cohort. And only when they were -- 3 they filled scripts that had the exposure or the 4 putative exposure was when they then started 5 contributing time to the cohort that had it, and so 6 that they note there limits immortal time bias, and so 7 it's a more accurate way of evaluating it. 8 And so to get to your question, they took 9 into account when each patient would have started the 10 actual drug with the impurity, even if they didn't 11 start it right from the beginning of the timing of 12 their study design. 13 Does that make sense? 14 BY MR. SLATER: 15 Q. Let me just be clear as to what you 16 considered -- I forgot to cover this -- and then we'll 17 come back to this study. 18 In terms of your methodology, my 19 understanding is you looked at the epidemiology 20 regarding valsartan specifically, and that's the 21 Pottegard and Gomm studies. You also looked at dietary 22 studies, you looked at industrial or occupational 23 exposure studies, and you looked at animal studies. 24 Do I understand that correctly, and you</p>
<p style="text-align: right;">Page 215</p> <p>1 period? 2 MR. INSOGNA: Object to form. 3 A. I would have to review this, but I think 4 that was what they started with, if you look at Figure 5 2 in the paper, and then based on inclusion of being 6 eligible based on the criteria for the study, they 7 excluded a number of patients, like patients who had 8 previous cancer, et cetera, less than age 40, all that 9 kind of stuff, and so it's not all of those patients 10 that they identified that were in that range. 11 BY MR. SLATER: 12 Q. My question is different. 13 Did you evaluate whether or not valsartan 14 sold between September 2011 and June 2017 was 15 contaminated or whether it started to be contaminated 16 later for some or all the manufacturers at issue? 17 MR. INSOGNA: Object to form. 18 A. I think that it was a date in 2012. And 19 so the authors, if you look at their methods, they did 20 a number of things to ensure accuracy here in terms of 21 whether patients were taking the drug with or without a 22 potential impurity, and also when they started. 23 They -- so for example, if a patient was 24 on valsartan but not with a contaminated version, they</p>	<p style="text-align: right;">Page 217</p> <p>1 put that together, and that was what you considered in 2 reaching your opinions? 3 A. Yes, as we talked at the very beginning, I 4 also looked at the opinions of the plaintiff experts 5 and what their opinions were and what they were relying 6 on. 7 And then through my independent analysis, 8 the way I normally do any scientific question, based on 9 my experience, based on all my training on how to 10 assess a scientific question and to review the 11 literature, I then did exactly as you said. 12 I looked at the human epi, which I put at 13 the highest priority, since we're humans; and then 14 other ancillary support, which includes, as you pointed 15 out, the occupational exposures, which again are 16 surrogates of NDMA through occupations. 17 And then I'm sure we'll get to that, but 18 sort of not asking the direct question, as an oral 19 exposure but rather an inhaled, and then also the 20 dietary. We've talked about the limitations of those. 21 And then the animal studies, and we haven't really 22 pointed to that yet, but taking all of that into 23 account. 24 And again, using the human epi, these</p>

<p>Page 218</p> <p>1 studies here, as sort of the more weighted part of my 2 analysis, since they're actually asking the question 3 that I think we're all interested in, whereas all those 4 other studies are looking at surrogate questions using 5 surrogate assessments and estimations of exposure, so 6 they're far lower on the hierarchy of the evidence to 7 be used in such a case as this than the actual question 8 at hand, which we had two human epi data studies, which 9 are the two that we've been talking about.</p> <p>10 And I'm happy to answer any other 11 questions about it, but that's why I started with this 12 and focused on this.</p> <p>13 Q. I want -- let me ask the question again, 14 because there's a lot you put in there that I tried to 15 keep -- I didn't ask about. So let's go to my 16 question.</p> <p>17 I looked at your report. I looked at what 18 you took into account. I saw you evaluating the human 19 epi studies, specifically Pottegard and Gomm. You went 20 through dietary studies. You looked at 21 industrial/occupational exposure, and you looked at 22 animal studies.</p> <p>23 And that was the universe that you 24 evaluated in terms of data to come up with your</p>	<p>Page 220</p> <p>1 the various pills varied over the years at all? 2 A. The contamination levels varied by lot 3 over the years and by different company, according to 4 the FDA reports and the tables that are shown there. 5 They were not consistent.</p> <p>6 Q. Was the variation in the impurity levels 7 taken into account in Pottegard? 8 A. In a way, yes, because patients were doing 9 what was the reality, which was they were being exposed 10 to the question at hand, which is intermittent exposure 11 that more likely than not wasn't the highest level in 12 every patient for the whole time; which as we then 13 point out from the FDA's assessments, they were always 14 taking the worst-case scenario just to show that even 15 that was a minimal risk, but the more likely scenario 16 is that most patients weren't exposed to the highest 17 levels, and certainly not for every lot throughout the 18 duration of time.</p> <p>19 And so in a way, Pottegard exactly 20 accounts for that because it's the exact reality of 21 what was going on. So it's looking at the question 22 we're asking, not a hypothetical one of what if 23 somebody had the whole thing the whole time at the 24 highest dose, which we've all agreed is extremely</p>
<p>Page 219</p> <p>1 opinions; correct? 2 A. Yes.</p> <p>3 Q. And if I understand correctly, going a 4 step further, you basically did an analysis of the 5 weight of the evidence and put it all together to form 6 your opinion; correct?</p> <p>7 MR. INSOGNA: Object to form.</p> <p>8 A. Yeah, I looked at all of the evidence and 9 the pieces of the evidence from those various 10 categories, some pieces being much larger parts of the 11 puzzle, other pieces being much smaller parts but still 12 considered, and ultimately came to my opinion based on 13 the results.</p> <p>14 BY MR. SLATER:</p> <p>15 Q. When you talk about what you focused on 16 the most, that was again Pottegard and Gomm, which you 17 felt were on a much higher level and much different 18 from the rest of the evidence available; correct?</p> <p>19 A. Yes, for the reasons that I stated, since 20 they're much more relevant studies for the question at 21 hand.</p> <p>22 Q. Do you know if the -- I'm coming -- 23 rephrase. I'm going back to Pottegard now.</p> <p>24 Do you know if the contamination levels in</p>	<p>Page 221</p> <p>1 unlikely. 2 Q. You state in your report at the bottom of 3 Page 38, "No statistically significant associations 4 were reported between valsartan products potentially 5 containing NDMA and any type of cancer." 6 And then you refer to the primary 7 endpoint; correct? 8 A. Yes. Yes.</p> <p>9 Q. The fact that there were no statistically 10 significant associations between valsartan products 11 potentially containing NDMA and any type of cancer -- 12 why was that significant to you? 13 A. Because that's the question that I was 14 asked to assess, is that if there is an added risk, 15 which would be manifested by observing higher 16 incidences of cancer in the patients exposed to it 17 compared to those not.</p> <p>18 So with this assessment, which was the 19 primary endpoint, looking at any cancer, the answer was 20 no. That's probably the most important piece of 21 evidence of all the things considered, since it's the 22 exact question we're asking.</p> <p>23 Q. You then state at the top of Page 39, "In 24 subgroup secondary analyses by cancer type, there was</p>

<p style="text-align: right;">Page 222</p> <p>1 no individual cancer that had a statistically 2 significant association of valsartan products 3 potentially containing the NDMA impurity." 4 Why did -- why was that significant to 5 you? 6 A. Because as secondary analyses, we're 7 interested, of course, in are there specific cancers 8 that may or may not be associated with taking these 9 agents versus the agents without the impurity. 10 And so it's secondary because it's not the 11 primary analysis, it's not statistically designed to 12 answer that question definitively, but it's looking at 13 it because we have the data and potentially making sure 14 that there's no subgroup that might have some 15 association. 16 And in this case, that was not the case in 17 this particular study. 18 Q. Did you independently verify the 19 statistical analysis in Pottegard or any other study? 20 MR. INSOGNA: Object to form. 21 A. I didn't do any statistical analyses. I 22 can read a paper and understand what the statistics 23 mean, but I didn't confirm them or do any statistical 24 analyses.</p>	<p style="text-align: right;">Page 224</p> <p>1 important data to consider from human epi data from the 2 study. 3 In terms of the subgroups now, looking at 4 them, when you see -- if you were to see a subgroup 5 that showed a signal, we have to be cautious there. 6 And I think we get to that in the Gomm study, where -- 7 there's a concept called multiple testing in 8 statistics, where if you test things enough and you 9 slice the data enough and what might be referred to as 10 massaging the data to look at it in various ways, 11 eventually you may find something by chance. 12 And so that's exactly what a P value 13 actually is, in a sense, where we talk about a P value 14 of .05, in terms of what's statistically significant. 15 And so that's translated to what you're more familiar 16 with, is if it crosses one or not, a hazard ratio or 17 odds ratio or relative risk. 18 If it's crosses one, then it's not 19 statistically significant, and the P value is above .5. 20 And if it doesn't cross the one boundary, then it is 21 considered statistically significant, and the P value 22 is less than .05. But all that's saying is that you 23 may have a false positive, but it's a less than five 24 percent chance that it's false positive; okay?</p>
<p style="text-align: right;">Page 223</p> <p>1 BY MR. SLATER: 2 Q. And you're not a biostatistician? You 3 don't hold yourself out as an expert in biostatistics, 4 do you? 5 A. I have been trained in biostatistics, I 6 have a master's degree in it, but I don't hold myself 7 as a statistician. I can understand them. It's the 8 language that we speak in science, which is statistics, 9 to ask questions or hypotheses and determine if there 10 are -- the hypothesis can be accepted or not, as we 11 talked about earlier. 12 So -- but I don't hold myself out to be a 13 statistician. 14 Q. And again, you accepted the statistical 15 analyses in these studies? You didn't independently 16 verify; correct? 17 A. Correct. 18 Q. If there had been a statistically 19 significant association either to any cancer in general 20 or to a specific cancer, would that have been of 21 significance to you? 22 A. In a hypothetical world, if the primary 23 endpoint showed that there was a significant 24 correlation in all cancers, then that would be</p>	<p style="text-align: right;">Page 225</p> <p>1 One in 20, five percent of the -- so if 2 you look at 20 hypotheses, you will find one by chance, 3 by accident. That's what statistics is all about. And 4 we're allowing for that when we're doing studies like 5 this, and saying we're going to set the threshold at 6 being less than .05. 7 If we find an association, it's probably 8 real, but there's a five percent chance that it's false 9 positive. But then if you start looking at 20 10 different hypotheses, you're at risk of then really 11 finding something that's false positive. 12 So getting back to the subgroups now, if I 13 find an association in one of the many things I've 14 looked at, then you have to look at that a little bit 15 skeptical. And you note it, it's there, yet it's not 16 something that's definitive, and that would probably 17 require further independent validation in other cohorts 18 in other studies before one would just hang their hat 19 on that one finding. 20 So that's the difference with sort of 21 looking at the main question and then looking at a 22 whole bunch of subgroup analyses afterwards. 23 Q. So you're saying the subgroup -- rephrase. 24 Are you saying the subgroup analyses</p>

<p style="text-align: right;">Page 226</p> <p>1 shouldn't be considered?</p> <p>2 A. I don't think I said that. I said that</p> <p>3 their value and your ability to put as much weight on</p> <p>4 the finding is lower.</p> <p>5 And as an example, in many studies that</p> <p>6 look at a primary endpoint -- in many of my studies,</p> <p>7 their treatment and trying to improve survival -- and</p> <p>8 let's say the study is negative, this drug X doesn't</p> <p>9 improve survival in everybody enrolled; but in other</p> <p>10 analyses of man versus female, people above 60 versus</p> <p>11 less than 60, all kinds of different ways of looking at</p> <p>12 the people differently, are there difference among</p> <p>13 subgroups.</p> <p>14 Sometimes there's one value or two that</p> <p>15 showed that the drug worked, and so we'll look at that</p> <p>16 and we'll say, "That's interesting, maybe the drug</p> <p>17 works in just a subgroup of people," but we also say</p> <p>18 this is a subgroup analysis, and it's at risk for false</p> <p>19 positives, and that we'd have to test this</p> <p>20 independently prospectively, that question and that</p> <p>21 tumor type, to be -- to have any weight or to hang your</p> <p>22 hat on that finding, so to speak.</p> <p>23 And so we consider it, yes, we note it,</p> <p>24 yes, but we wouldn't act on it per se as much as we</p>	<p style="text-align: right;">Page 228</p> <p>1 your question is as opposed to all cancers, there was</p> <p>2 essentially no trend. It was like one, 1.09. It's</p> <p>3 essentially no difference.</p> <p>4 But if you're looking at subgroups of</p> <p>5 cancers, you can see that some cancers look to the left</p> <p>6 of the force plot in Figure 3 of that paper, which</p> <p>7 suggest that it was protective, it was protective of</p> <p>8 taking these drugs compared to not taking impurity, and</p> <p>9 in other cancers there were trends the other direction</p> <p>10 which suggested that it was -- that it was consistent</p> <p>11 with an association.</p> <p>12 And so the answer is yes, there were</p> <p>13 trends both ways. Trends means by definition in</p> <p>14 statistics not statistically significant, but trends</p> <p>15 towards one way or the other.</p> <p>16 Q. First let's define for which cancers there</p> <p>17 were trends towards statistical significance.</p> <p>18 One would be colorectal cancer; right?</p> <p>19 A. Colorectal cancer was 1.46 trend to the</p> <p>20 right we would say on a force plot, but also the lower</p> <p>21 boundary was .79, the other side of one.</p> <p>22 Q. Am I correct that there was a trend</p> <p>23 towards significance for colorectal cancer?</p> <p>24 A. Depends on what you define as trend.</p>
<p style="text-align: right;">Page 227</p> <p>1 would a primary endpoint of the same study.</p> <p>2 Q. You pointed out with regard to Pottegard</p> <p>3 that on the subgroup secondary analyses by cancer type</p> <p>4 there was no statistically significant association.</p> <p>5 You were stating that as part of the</p> <p>6 evidence that you're relying on to say that the NDMA in</p> <p>7 these pills, in your opinion, likely didn't increase</p> <p>8 the risk to the people that got cancer and are now</p> <p>9 saying they got cancer from the pills; right?</p> <p>10 MR. INSOGNA: Object to form.</p> <p>11 A. That's right. And remember, we go back --</p> <p>12 BY MR. SLATER:</p> <p>13 Q. That's right. That's all I asked you,</p> <p>14 though, Doctor. I literally just asked you yes or no.</p> <p>15 You confirmed it. I didn't ask for an explanation.</p> <p>16 A. Okay.</p> <p>17 Q. Now, in looking at this -- actually, let</p> <p>18 me find my note. One second.</p> <p>19 Looking now at Pottegard, were there</p> <p>20 trends towards statistically significant association</p> <p>21 for any cancers?</p> <p>22 A. I'm just looking at it real quick.</p> <p>23 There were -- if you're looking at actual</p> <p>24 cancers, there were -- when you looked at subgroups,</p>	<p style="text-align: right;">Page 229</p> <p>1 Often we define trend as it trends towards one way with</p> <p>2 a higher ratio, relative risk, and that the P value</p> <p>3 approaches .05, like maybe it's .06 or .07 or .08, not</p> <p>4 if it's .2 or .3 and it trends to that side from the</p> <p>5 hazard ratio.</p> <p>6 So can you clarify what you mean by trend?</p> <p>7 Because this is not trending statistically. .79 is a</p> <p>8 very low bar, low boundary. It's not .98 as the lower</p> <p>9 bound or .99 as the lower bound. It's .79.</p> <p>10 Q. Does the hazard ratio of 1.46 hold any</p> <p>11 significance?</p> <p>12 A. It's the point estimate hazard ratio,</p> <p>13 meaning that's the point estimate of the 51 patients</p> <p>14 that were -- that had events with colorectal cancer.</p> <p>15 Q. Was there a trend towards statistical</p> <p>16 significance for uterine cancer?</p> <p>17 A. Uterine cancer you can see was 1.81 hazard</p> <p>18 ratio as a point estimate with confidence interval of</p> <p>19 .55 to 5.9 with 15 events.</p> <p>20 The way I interpret that is that's not a</p> <p>21 statistical trend. That's spurious with wide range,</p> <p>22 wide confidence intervals with very few events.</p> <p>23 Q. One second. In the abstract -- we'll just</p> <p>24 go with that, because it's just easier to focus on, on</p>

<p style="text-align: right;">Page 230</p> <p>1 the front page of the article.</p> <p>2 In the results section, the authors</p> <p>3 discuss what we just talked about, and they say, "For</p> <p>4 single cancer outcomes, increases in risk were observed</p> <p>5 for colorectal cancer, hazard ratio 1.46, 95 percent</p> <p>6 confidence interval, 0.79 to 2.73, and for uterine</p> <p>7 cancer, 1.81, 0.55 to 5.90, although with wide</p> <p>8 confidence intervals that included the null."</p> <p>9 That's what we just discussed; correct?</p> <p>10 A. Yes.</p> <p>11 Q. Turn if you could now to the fourth page</p> <p>12 of the article.</p> <p>13 A. Page 4?</p> <p>14 Q. I don't have the page numbers on my copy.</p> <p>15 I'm just not seeing them. So it's the fourth page,</p> <p>16 though. It has -- the discussion starts on this page.</p> <p>17 A. Yes.</p> <p>18 Q. And they discuss the single cancer</p> <p>19 outcomes again.</p> <p>20 You see that in the left-hand column;</p> <p>21 right? Right under Figure 2.</p> <p>22 A. Which figure?</p> <p>23 Q. Figure 2.</p> <p>24 A. Figure 2? The flow chart of cohort</p>	<p style="text-align: right;">Page 232</p> <p>1 a prevalent user and an incident user?</p> <p>2 A. I believe a prevalent user was one who</p> <p>3 started on blood pressure -- who were on the valsartan</p> <p>4 at the time of the starting dates, as opposed to an</p> <p>5 incident user who started at some point later.</p> <p>6 Q. And a prevalent user could have been on</p> <p>7 the medication and then could have stopped a week after</p> <p>8 the study period was established; right?</p> <p>9 A. No, that doesn't sound right. It's --</p> <p>10 patients who were taking the medications for the</p> <p>11 duration that they were taking them were included. So</p> <p>12 patient time and follow-up, what you see there,</p> <p>13 incorporates how long a patient was on the drug or not.</p> <p>14 All prevalent -- incidences -- who was on it to begin</p> <p>15 with versus not.</p> <p>16 Q. Right. A prevalent user was someone who</p> <p>17 was already using the medication before the study</p> <p>18 period began; right?</p> <p>19 A. And were on it at the beginning of the</p> <p>20 study period, yes. That's --</p> <p>21 Q. Right. And then --</p> <p>22 A. Yeah.</p> <p>23 Q. Right. And then could have stopped taking</p> <p>24 the medication shortly thereafter; right?</p>
<p style="text-align: right;">Page 231</p> <p>1 selection of Danish users?</p> <p>2 Q. Yes.</p> <p>3 A. Yes. Okay, I see that.</p> <p>4 Q. Right under that, it talks again about</p> <p>5 what we just discussed, the increased risks seen for</p> <p>6 certain single cancer outcomes; right?</p> <p>7 A. It says that, and it says also did not</p> <p>8 reach statistical significance, yes.</p> <p>9 Q. Right. They said increased risks were</p> <p>10 seen, but did not reach statistical significance?</p> <p>11 A. That's how they worded it, yes.</p> <p>12 Q. The next paragraph, they say, "Results</p> <p>13 comparable to the main analyses were found when we</p> <p>14 stratified by sex and age, whereas a</p> <p>15 stronger association was seen when we restricted to</p> <p>16 incident users during the study period, hazard ratio</p> <p>17 1.58, 95 percent confidence interval, 0.99 to 2.52,</p> <p>18 compared with prevalent users at the beginning of the</p> <p>19 study period."</p> <p>20 0.91 was the hazard ratio. 0.66 to 1.25,</p> <p>21 and that's reflected in Figure 4.</p> <p>22 Do you see that?</p> <p>23 A. Yes, I do.</p> <p>24 Q. Did you understand the difference between</p>	<p style="text-align: right;">Page 233</p> <p>1 A. Some could, but they would be censored in</p> <p>2 terms of their follow-up after that point in terms of</p> <p>3 patient follow-up usage of the drug.</p> <p>4 Q. What do you mean, censored?</p> <p>5 A. Like they would be -- they would have</p> <p>6 accounted for the time they were on the drug, and then</p> <p>7 they would follow them for any incident cancers, but</p> <p>8 they wouldn't say that they were on it for the duration</p> <p>9 of the cohort time. For --</p> <p>10 Q. Well, the study didn't require somebody to</p> <p>11 stay on the drug for the entire cohort time, it just</p> <p>12 required that they fill a prescription during the study</p> <p>13 period, one prescription; right?</p> <p>14 A. Right. And the same thing could be for</p> <p>15 the incident user who could have started three weeks</p> <p>16 into the cohort and then stopped three weeks later. I</p> <p>17 mean, that argument would apply to either group that</p> <p>18 you just said.</p> <p>19 Q. Did you discuss this analysis that I just</p> <p>20 read to you where the lower bound was 0.99? And</p> <p>21 that's -- if it was one, you would say this was</p> <p>22 statistically significant; right?</p> <p>23 MR. INSOGNA: Object to form. Compound.</p> <p>24 A. Well, I think this gets to the question of</p>

<p style="text-align: right;">Page 234</p> <p>1 multiple testing, multiple hypothesis testing, where if 2 you're looking at all of these questions you're asking, 3 you've asked many questions now, and so that is why 4 this has much less weight compared to the original 5 question of the main -- of all cancers. 6 But did I talk about every one of these in 7 the paper? No. I think I summarized and said that 8 overall that there was no difference in the main 9 analysis, and that in secondary analyses that there was 10 no statistically significant association. 11 I mean, I didn't pick out each one 12 individually, though. No. 13 BY MR. SLATER: 14 Q. You didn't analyze this part of the study 15 at all in your report? It's not mentioned; right? 16 MR. INSOGNA: Object to form. 17 A. I just mentioned that all secondary 18 analyses done were not statistically significant, which 19 sort of encompasses all of those subgroups in Figure 3 20 and 4. 21 BY MR. SLATER: 22 Q. If 0.99 at the lower bound of this 23 confidence interval had come out as 1.00, would you 24 have then talked about it?</p>	<p style="text-align: right;">Page 236</p> <p>1 alternative hypothesis is that they do, and so I need 2 to look at data to be able to reject the null 3 hypothesis and accept the alternative. 4 And what that means is is there a 5 statistically significant finding in my main question 6 or not, which there was not, and we will entertain 7 subgroups to see if there are signals that maybe should 8 be followed up on in future analyses, et cetera. 9 And in this case, there was no 10 statistically significant signal -- any of the 11 subgroups analyzed. 12 BY MR. SLATER: 13 Q. Would you agree with me that the follow-up 14 period was too short to draw any definite conclusions? 15 MR. INSOGNA: Object to form. 16 A. I think that the conclusions of the 17 authors are appropriate, which is -- and the 18 limitations that they note are that at the time of the 19 study, which was the follow-up that they were able to 20 have, given this was relatively recent, was assessing 21 what the risk is after this much time, which is I think 22 very relevant to the questions being asked of us, 23 because this is the time point at which plaintiffs are 24 alleging their cancer is being caused by this. So it's</p>
<p style="text-align: right;">Page 235</p> <p>1 MR. INSOGNA: Object to form. Assumes 2 facts. 3 A. You know, in that hypothetical scenario, 4 which I think there is one such like that in Gomm, I 5 did point it out, as did the authors, to point out that 6 there was a statistical finding, and we're going to get 7 to that, I am sure, about one of the subgroup studies. 8 But I guess -- I think bringing you back 9 to how statistics works is that yeah, if you keep 10 looking at things, you'll find something, and you have 11 to be cautious that it's just by chance. 12 And so overall in this particular paper, 13 which you're asking me about, which I wrote about, 14 there is no statistical significant one, and that's 15 what I said, period. 16 BY MR. SLATER: 17 Q. So you thought it was important that there 18 was no statistically significant outcomes either in the 19 primary or secondary analyses; right? 20 MR. INSOGNA: Form. 21 A. That was an important finding because, 22 remember, my question is when I'm looking at the 23 hypothesis, which is these drugs increase cancer risk, 24 the null analysis is that they don't, and the</p>	<p style="text-align: right;">Page 237</p> <p>1 very relevant. 2 But at the same time, there are 3 limitations to suggest -- and may point out here we 4 don't know what this means from a longer perspective, 5 we have to follow this longer. 6 BY MR. SLATER: 7 Q. So is the answer to my question yes? 8 MR. INSOGNA: Object to form. 9 A. Can you state the question again, please? 10 BY MR. SLATER: 11 Q. Would you agree that the follow-up period 12 was too short to draw any definite conclusions? 13 A. Based -- about what question? About the 14 question is there short-term risk? No, there's 15 adequate follow-up. We looked at it. There was no 16 short-term risk. This is what the cases are being 17 asked of us at the moment. 18 Is it adequate to ask the question about 19 longer term, 10, 15, 20 years later? No, of course 20 not. We didn't follow them that long. 21 Q. For what carcinogens would you expect to 22 see a signal in a cohort study conducted about four 23 years after exposure? 24 A. Not many, in fact. It depends on the</p>

<p style="text-align: right;">Page 238</p> <p>1 dose, and it depends on the duration that they're 2 taking it, of course. But I think based on many of our 3 reports that you've seen, you understand that the 4 carcinogenesis of cancer, which is why I went into that 5 as a background, is it takes decades at the time of the 6 initiation of a cancer to the time it manifests. 7 And so right, an exposure, only three to 8 four years of follow-up from that exposure, if the 9 alleged risk is that it causes the cancer and starts 10 it, then it would be very implausible, especially at 11 these trace levels that we're talking about here. 12 We're not talking about astronomical doses. 13 Q. Even with these what you call not 14 astronomical doses, and even with this short-term 15 follow-up period, increase in risk was seen for certain 16 specific cancers; right? 17 A. -- human epi data? 18 Q. We went through this already. The 19 colorectal cancer and uterine cancer, for example, 20 showed increased risk; right? 21 A. Nonstatistically increased risk that are 22 random variation from looking at subgroups -- a small 23 number. Yes. 24 Q. Doctor -- I've really tried to be patient.</p>	<p style="text-align: right;">Page 240</p> <p>1 about single cancer outcomes and studies with longer 2 follow-up are needed to assess long-term cancer risk." 3 Do you agree with that description? 4 A. Yes. Yes. 5 Q. When they refer to uncertainty persists 6 about single cancer outcomes, that means that this 7 study certainly does not rule out a causal association; 8 right? 9 MR. INSOGNA: Object to form. 10 A. That would be a correct interpretation, 11 that it doesn't -- it doesn't rule it out that there's 12 a causation, but it doesn't -- certainly doesn't rule 13 it in any way. If anything, the evidence suggests 14 against. 15 BY MR. SLATER: 16 Q. If you could look in the introduction of 17 the study, just a little further down from we were just 18 reading in that right-hand column of the first page of 19 the article. 20 A. Yes. 21 Q. The second paragraph, the second sentence 22 says, "NDMA is one of the most well-characterized and 23 most potent animal carcinogens known." I want to stop 24 there.</p>
<p style="text-align: right;">Page 239</p> <p>1 I'd appreciate if you just answer my question. I 2 didn't ask you about -- you keep throwing in things I'm 3 not asking about. Your -- the lawyer sitting next to 4 you can question you to his heart's content when I'm 5 done. 6 MR. INSOGNA: Adam, that's absolutely not 7 accurate. He responded to your question. That you 8 don't like the answer does not mean it was not an 9 answer. 10 MR. SLATER: Okay. 11 BY MR. SLATER: 12 Q. With what you just termed not astronomical 13 doses of NDMA, we still saw increase in risk as 14 reflected in the article for at least colorectal cancer 15 and uterine cancer, as discussed in the abstract? 16 That's what the words in the study say; 17 correct? 18 A. The words in the study say a 19 nonstatistically increase in risk, yes. That's all I 20 said when I responded. 21 Q. Looking at the conclusion, the authors 22 state, "The results do not imply a markedly increased 23 short-term overall risk of cancer in users of valsartan 24 contaminated with NDMA. However, uncertainty persists</p>	<p style="text-align: right;">Page 241</p> <p>1 Do you agree with that statement? 2 A. It doesn't say anything about the dosing 3 and stuff, but we know that at very high doses it does 4 cause cancers in various models like rats, yes. Way -- 5 Q. I'll try again. 6 A. Way higher than the doses that we're 7 talking about here. 8 Q. Yeah, but that's not what I asked you, so 9 let's try it again. 10 This says in the second paragraph under 11 the introduction, "NDMA is one of the most 12 well-characterized and most potent animal carcinogens 13 known." 14 Do you agree with that statement? 15 MR. INSOGNA: Object to form. Asked and 16 answered. 17 A. I answered it with the qualification, but 18 it does say that right there, yes. 19 BY MR. SLATER: 20 Q. And you agree with it? It's a true 21 statement; right? 22 MR. INSOGNA: Same objection. 23 A. With the qualifications, because just 24 agreeing to that statement can be very misleading.</p>

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1 BY MR. SLATER:
 2 Q. Do you think this article is misleading?
 3 A. I think that that statement without
 4 qualifying that can be very misleading.
 5 Q. Is it scientifically accepted in the
 6 scientific community that NDMA is one of the most
 7 well-characterized and most potent animal carcinogens
 8 known?
 9 A. At high doses, no.
 10 Q. You're saying no, that's not understood in
 11 the scientific community?
 12 A. No, excuse me. At high doses, that is
 13 accepted, yes. That it's a potent carcinogen at very
 14 high doses.
 15 Q. So you think at low doses NDMA is not
 16 considered a potent carcinogen?
 17 A. No. We can talk about that, but you can
 18 see it in all the datasets that in some -- in some
 19 studies, the control are not getting any NDMA to have
 20 more cancers than at the low doses.
 21 So in other words, no, it's not potent at
 22 all at low doses.
 23 Q. Which study is that?
 24 A. The Keto (ph) studies, for example, are

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1 probably the ones fresh in my mind.
 2 Q. This says in the second paragraph under
 3 the introduction, "NDMA is one of the most
 4 well-characterized and most potent animal carcinogens
 5 known and has been shown to be a potent carcinogen
 6 across all species that have been investigated, both as
 7 single doses and with long-term exposure to lower
 8 quantities."
 9 Do you see that statement?
 10 A. At single doses, yes. I think we'll be
 11 talking about astronomically high doses of that agent.
 12 Q. Doctor, all I asked you is if you saw the
 13 statement.
 14 A. I saw the statement, yes.
 15 Q. So why -- I don't understand why you're
 16 arguing something I didn't even ask you.
 17 A. You asked if I agreed with it.
 18 Q. No, I didn't.
 19 MR. INSOGNA: You don't need to argue --
 20 there's no --
 21 BY MR. SLATER:
 22 Q. Actually, all I said was do you see that
 23 statement.
 24 A. I see the statement.

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1 Q. It's a true statement; correct?
 2 MR. INSOGNA: Object to form.
 3 A. With the qualifications that I mentioned.
 4 It can be toxic at very high single doses, yes, which
 5 is not relevant to what I've been asked to opine on
 6 here.
 7 BY MR. SLATER:
 8 Q. I'd have to ask you again. I mean,
 9 Doctor, just --
 10 MR. SLATER: We're never getting done
 11 today. I can tell you that right now, counsel. I'm
 12 going to end up having to continue through tomorrow.
 13 We're going to have to figure out a time, because I'm
 14 just not getting anywhere now. And it's been going on
 15 for hours.
 16 MR. INSOGNA: He is answering your
 17 questions. You just don't like the answers. You --
 18 MR. SLATER: Counsel, I don't like when
 19 people say you don't like the answer. It's not a
 20 question of liking or not liking the answer. I'd
 21 prefer it just be responsive. That's all I'm asking.
 22 MR. INSOGNA: I think he's answered --
 23 MR. SLATER: I've been very patient,
 24 unbelievably patient through this deposition. I'll

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1 continue to be so. But if I ask a straightforward
 2 question and the witness continually provides
 3 disclaimers and explanations rather than a yes or a no,
 4 then I have to just keep coming back.
 5 This is an expert. This isn't some
 6 regular layperson witness. We need to be able to
 7 proceed in an orderly way.
 8 MR. INSOGNA: Ask your question.
 9 BY MR. SLATER:
 10 Q. This states in the second paragraph under
 11 the introduction, "NDMA is one of the most
 12 well-characterized and most potent animal carcinogens
 13 known and has been shown to be a potent carcinogen
 14 across all species that have been investigated, both as
 15 single doses and with long-term exposure to lower
 16 quantities."
 17 That statement is found in a study that
 18 you're relying on heavily for your opinion in this
 19 case; correct?
 20 MR. INSOGNA: Object to form.
 21 A. The reference there to Number 5 is not to
 22 the Keto study that I just mentioned. If that's your
 23 question, no.
 24 BY MR. SLATER:

<p style="text-align: right;">Page 246</p> <p>1 Q. I'm talking about this study, the 2 Pottegard study that we're asking about. 3 That's the one you're relying on heavily; 4 right? 5 A. Oh, for the human epidemiological data? 6 Yes. I thought you were talking about that sentence 7 that has Reference 5 to the -- and you were insinuating 8 it was to the data I was relying on for animal data. 9 It's not. 10 Q. I actually wasn't insinuating that. 11 With re -- I'll do it again. 12 In the introduction, right-hand column, 13 second paragraph, it says in part, "NDMA is one of the 14 most well-characterized and most potent animal 15 carcinogens known and has been shown to be a potent 16 carcinogen across all species that have been 17 investigated, both as single doses and with long-term 18 exposure to lower quantities." 19 That statement is found here in the 20 Pottegard study, which you're relying on heavily for 21 your opinion; correct? 22 A. I'm relying on the results of the study, 23 yes, not that statement in the introduction, no. 24 Q. It continues, "Although no in vivo data</p>	<p style="text-align: right;">Page 248</p> <p>1 Q. The principal findings starts out, "Our 2 estimates pertain to early cancer risk associated with 3 exposure to NDMA through contaminated valsartan 4 products and should not be interpreted as evidence 5 against NDMA being carcinogenic to humans in general. 6 At most, our findings suggest that the level of NDMA 7 exposure achieved through valsartan products do not 8 translate into a substantially increased short-term 9 cancer risk." 10 Do you see what I just read? 11 A. Yes. 12 Q. Did you anywhere in your report reference 13 or comment on what I just read? 14 A. I believe so, yes. 15 Q. Or to Pottegard? 16 A. Yes. 17 Q. Where? 18 A. When I -- on Page 40 at the top of my 19 report, the first sentence. "While each of these 20 studies notes the obvious limitation of a shortened 21 follow-up period" -- the period is actually more 22 closely reflective to what we're talking about now, 23 which I also said a few questions ago as well. 24 Q. Did you say in your report that the</p>
<p style="text-align: right;">Page 247</p> <p>1 are available for humans, NDMA seems to be metabolized 2 similarly in human tissue and rodent tissue." 3 That is also stated; correct? 4 A. Yes. 5 Q. You don't disagree with that; right? 6 A. Not necessarily. 7 Q. Let's go back where we were talking just 8 before about incident users versus prevalent users, 9 just above the discussion section; okay? 10 A. Yes. 11 Q. If the lower range of that analysis had 12 been 1.01 instead of .99, that would have achieved 13 statistical significance; correct? 14 A. That is a correct statement. 15 Q. So would it be fair to say that for 16 incident users, people who started taking the drug 17 during the time in question, there was almost a 60 18 percent increased rate of cancer, and this almost 19 reached statistical significance? 20 A. Almost reached statistical significance 21 would be an appropriate summary, yes. 22 Q. Let's go, if we could, to the sixth page 23 of the article, the principal findings. 24 A. Yes.</p>	<p style="text-align: right;">Page 249</p> <p>1 results of this study should not be interpreted as 2 evidence against NDMA being carcinogenic to humans in 3 general? 4 A. I didn't say that, no. 5 Q. And you would agree with me that the 6 results of this study should not be interpreted as 7 evidence against NDMA being carcinogenic to humans in 8 general? 9 You would agree with that; right? 10 A. With long-term follow -- 11 MR. INSOGNA: Object to form. 12 A. With long-term follow-up, I agree with 13 that, yes. You had asked the question with respect to 14 the follow-up that it did do, which is relevant to 15 current cases I've mentioned. 16 BY MR. SLATER: 17 Q. Going down to the bottom of that 18 paragraph. They talk about the single cancer outcomes, 19 in particular colorectal and uterine cancer, and they 20 say that, "This clearly highlights that our study 21 cannot confidently rule out an increased risk from 22 exposure to NDMA." 23 Correct? 24 A. Yes, they say that.</p>

<p style="text-align: right;">Page 250</p> <p>1 Q. And you agree with that; right?</p> <p>2 A. Yeah, I think that that's a very fair</p> <p>3 statement, as we've been saying, is that these data</p> <p>4 that we're looking at subgroups are exactly that.</p> <p>5 They're subgroup analyses looking at smaller subsets.</p> <p>6 There's no obvious or large -- which I</p> <p>7 think they also point out throughout this paper and the</p> <p>8 other paper -- that there's no obvious and large</p> <p>9 magnitude benefit -- or effect, excuse me, but that</p> <p>10 smaller effect sizes, and because these are subgroups,</p> <p>11 we can't rule out a possible association, but there's</p> <p>12 no evidence from these data that there is.</p> <p>13 Q. Further down in the second paragraph under</p> <p>14 the principal findings, the authors refer to the</p> <p>15 uncertainty about the actual NDMA content of valsartan</p> <p>16 products.</p> <p>17 Do you see that?</p> <p>18 A. I remember reading about that. Where did</p> <p>19 we -- where is that again?</p> <p>20 Q. It's four lines up from the bottom of the</p> <p>21 page.</p> <p>22 A. Yes.</p> <p>23 Q. That uncertainty about the actual NDMA</p> <p>24 content of the valsartan products that the people in</p>	<p style="text-align: right;">Page 252</p> <p>1 Q. The people that they assumed were probably</p> <p>2 exposed to NDMA were those who took a product that was</p> <p>3 manufactured by ZHP at some point; right?</p> <p>4 A. I believe so. I'd have to confirm that</p> <p>5 here again, but that sounds very familiar, yes.</p> <p>6 Q. And that means that somebody could have</p> <p>7 filled one prescription of ZHP-manufactured valsartan</p> <p>8 and then taken pills manufactured by other</p> <p>9 manufacturers the entire rest of the study, but they</p> <p>10 would end up in the side of the study that's assumed to</p> <p>11 have been exposed to NDMA; right?</p> <p>12 MR. INSOGNA: Form.</p> <p>13 A. I think we talked about that earlier. I</p> <p>14 think that they had to -- they were trying to reflect</p> <p>15 what was happening in reality; and that the likelihood,</p> <p>16 as you point out very well, is that a given patient is</p> <p>17 very unlikely to have been unlucky to have gone a lot</p> <p>18 with the highest levels the whole time.</p> <p>19 But if that happened, they would be</p> <p>20 included here, but to the extent that it did happen,</p> <p>21 this was reflecting what was actually happening. So</p> <p>22 this asks the question that's very relevant to us, is</p> <p>23 do patients who got some do worse than those who</p> <p>24 didn't.</p>
<p style="text-align: right;">Page 251</p> <p>1 this study took has to raise some questions; correct?</p> <p>2 MR. INSOGNA: Object to form.</p> <p>3 A. It's a known limitation, in that despite</p> <p>4 all efforts that were made to try and quantify that was</p> <p>5 being done and what patients were getting what and</p> <p>6 when, there was always the possibility that -- I mean,</p> <p>7 especially in a group that was classified as possible</p> <p>8 as opposed to probable -- that they may not, but there</p> <p>9 were sensitivity analyses in these studies to sort of</p> <p>10 address that by excluding the ones that were possible</p> <p>11 and looking at just those that are probable.</p> <p>12 There were other sensitivity analyses that</p> <p>13 cut off the date from if they were only on it for one</p> <p>14 year to six months or two years, to see if there were</p> <p>15 any major differences. So those types of sensitivity</p> <p>16 analyses that are done in these studies are trying to</p> <p>17 assess some of the limitations to make sure that there</p> <p>18 isn't something being missed, to the best of one's</p> <p>19 ability.</p> <p>20 But despite that, to your question, that</p> <p>21 they're noting here appropriately that there's still</p> <p>22 going to be some uncertainty, like there is with any</p> <p>23 study of its kind like this.</p> <p>24 BY MR. SLATER:</p>	<p style="text-align: right;">Page 253</p> <p>1 BY MR. SLATER:</p> <p>2 Q. So coming back to my question, which I'd</p> <p>3 appreciate if you could answer.</p> <p>4 Somebody who was placed on the side of the</p> <p>5 study as having been assumed to be exposed to NDMA</p> <p>6 could have filled one prescription of ZHP valsartan one</p> <p>7 time, and then the rest of the study period taken</p> <p>8 valsartan manufactured by manufacturers that did not</p> <p>9 have NDMA contamination, but that person would be on</p> <p>10 the NDMA side of the study; correct?</p> <p>11 MR. INSOGNA: Object to form.</p> <p>12 A. They would have to be, because now they've</p> <p>13 had exposure to the putative exposure. So yeah.</p> <p>14 BY MR. SLATER:</p> <p>15 Q. So the answer to my question is yes?</p> <p>16 A. Yes, patients who were exposed to the</p> <p>17 probable or possible were then included in that group,</p> <p>18 because they were in that group.</p> <p>19 Q. You would agree that somebody who took one</p> <p>20 prescription of ZHP valsartan that was contaminated</p> <p>21 with NDMA would have received a lower dose than</p> <p>22 somebody who filled prescriptions of ZHP valsartan,</p> <p>23 let's say, for two full years; right?</p> <p>24 A. In the main analysis they did that. They</p>

<p style="text-align: right;">Page 254</p> <p>1 lumped them together as being exposed. But if you read 2 on Page 2 in the methods on the right, it said they 3 further stratified by the time of cumulative dose of 4 these filled prescriptions with NDMA and put them into 5 categories based on the amounts that they were exposed 6 to. So they tried to account for what you're getting 7 at, basically.</p> <p>8 And then if you look at Table 2, they're 9 looking at by that cumulative exposure, which is 10 assessing exactly what you're asking, to say if people 11 that were on more did worse than those who didn't, 12 which was not the case.</p> <p>13 Q. You're saying people who took the 14 medication for a longer period of time; right?</p> <p>15 A. For more cumulative exposure to the NDMA 16 exposed lots. That's less than 20,000, greater than 17 50,000, or in between. Those are the three categories. 18 So they are accounting for what you're asking about.</p> <p>19 And you can see on the right there, 20 especially after when you look at all the adjustments 21 that they did that there's no difference between those 22 who got less versus more versus intermediate, in terms 23 of their assessment, in terms of hazard ratio. All of 24 them cross one, one of them is actually lower than one,</p>	<p style="text-align: right;">Page 256</p> <p>1 identified to be manufactured by ZHP, and so they were 2 able to classify by that, versus if you read the next 3 sentence it talks about other products that were 4 classified as possibly contaminated, and they had ZHP 5 and other companies.</p> <p>6 And so they categorized by those two main 7 categories or not, those three subgroups.</p> <p>8 BY MR. SLATER:</p> <p>9 Q. But again -- but again, when doing the 10 stratification, they didn't go prescription by 11 prescription, say ZHP, not ZHP? They didn't do that 12 analysis; correct?</p> <p>13 If you were in the ZHP side of the study, 14 meaning you filled one prescription, that's how you got 15 in and that's how you were analyzed; right?</p> <p>16 A. In the all-comer group, yes, that's how 17 they were analyzed, but when they were looking at Table 18 2 they were looking at -- you could see a never-user or 19 an ever-exposure, the top two rows.</p> <p>20 But then they're looking at the cumulative 21 exposure by looking at the amount that they actually 22 were exposed to.</p> <p>23 Q. Well, they have no idea what they were 24 exposed to? They don't have the exposures levels lot</p>
<p style="text-align: right;">Page 255</p> <p>1 and the effect sizes, the point estimates, are 1.15, 2 1.11.</p> <p>3 Q. Are you suggesting that they went through 4 every single prescription filled by each person and 5 stratified based on an analysis of every single 6 prescription for each person?</p> <p>7 A. If you read this page, that they said they 8 further stratified exposed person time by cumulative 9 dose from filled prescriptions of potentially 10 NDMA-containing valsartan tablets.</p> <p>11 So the answer to that is they made an 12 attempt to do that at every prescription. That was the 13 strength of the study, is that they have the records of 14 when people went and picked up their scripts.</p> <p>15 Q. When they did so, did they distinguish 16 between whether or not the pills were manufactured by 17 ZHP, if somebody was in the assumed NDMA-contaminated 18 part of the study, or did they just go by the overall 19 filled prescriptions without analysis of whether it was 20 ZHP or not in every single prescription?</p> <p>21 MR. INSOGNA: Object to form.</p> <p>22 A. The answer to your question is earlier in 23 that same paragraph, where it says that they were able 24 to identify 128 unique drug products that were</p>	<p style="text-align: right;">Page 257</p> <p>1 by lot, so there's no way for them to know that; 2 correct?</p> <p>3 MR. INSOGNA: Object to form.</p> <p>4 A. They're looking at the estimated by the 5 pills here, further down in the same methods, where 6 they were estimating based upon the amount of -- the 7 drug amounts that they were taking.</p> <p>8 BY MR. SLATER:</p> <p>9 Q. So if somebody only filled one 10 prescription of ZHP and then took other manufacturers 11 that were uncontaminated, you're saying that they only 12 counted for that person the one prescription of ZHP, 13 even though they were on the presumed contaminated side 14 of the study?</p> <p>15 MR. INSOGNA: Object to form.</p> <p>16 BY MR. SLATER:</p> <p>17 Q. Because I didn't see that they did the 18 analysis to that level of granularity. I thought that 19 once you got on that side, you were analyzed as you 20 were exposed to contaminated pills.</p> <p>21 A. I'm looking at this sentence, and the way 22 I read it is we further stratified NDMA exposed person 23 time by cumulative dose from filled prescriptions of 24 potentially NDMA-containing valsartan tablets, which</p>

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1 they knew because they filled the script and they were
2 able to define which products were from ZHP.
3 So I read it as they would add up all of
4 the ones that they took from that company, and if they
5 met, then they would categorize them into those three
6 groups.
7 And then the rows in Table 2, they looked
8 at it whether they never used it versus used it, which
9 was the main analysis; and then they looked at the
10 cumulative exposure to the NDMA pills.
11 That's the way I look -- that's the way I
12 see what they wrote here.
13 Q. It doesn't actually say that they did what
14 you're saying? That's what you're assuming; correct?
15 MR. INSOGNA: Object to form.
16 A. That's how I read that -- I read that now,
17 even -- that's how it reads to me. In a question like
18 this, maybe I would look for a clarification.
19 BY MR. SLATER:
20 Q. Now looking at the top of that page where
21 you were just reading, where they talked about the
22 other side of the study, the other group which was the
23 people they classified as unlikely to be contaminated
24 with NDMA.

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1 You see that?
2 A. I'm sorry. Where?
3 Q. At the top of the second page of the
4 study, the other side of the study, the people who were
5 assumed not to have been taking valsartan --
6 A. Yes.
7 Q. -- that was contaminated with NDMA.
8 Those were people who took pills that were
9 not manufactured by ZHP; correct?
10 A. In the never group, yes. Or from that
11 second category, possibly, which included ZHP and they
12 call it other companies, but that doesn't specify which
13 companies.
14 Q. Well, if you took it from ZHP and another
15 company, you ended up on the contaminated side of the
16 study; right?
17 A. Yes. Yes.
18 Q. This side of the study, the never side of
19 the study, included people who didn't take any
20 ZHP-manufactured valsartan? That was that group;
21 right?
22 A. Or the other companies, is the way that I
23 read it, which is that intermediate group of possibly
24 exposed. Because you read here on the same page, where

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1 it goes -- just one sentence before the one I quoted
2 before, which is in the main analysis we pooled
3 together prescriptions classified as probably and
4 possibly contaminated as being those exposed, compared
5 to of course those who weren't in those two groups.
6 And right before that, it's defining what
7 those two groups are, and possibly included the ZHP and
8 those from other companies.
9 Q. As long as they filled the ZHP
10 prescription; right?
11 A. Or they fit into that category as defined
12 here, yes.
13 Q. The other side of the study was people who
14 did not take any ZHP; right?
15 A. And my understanding is -- or if those
16 other companies that are listed in that possibly
17 contaminated intermediate group.
18 Q. And where do you see that list?
19 A. The list?
20 Q. The list of the other companies that were
21 considered to be contaminated. I didn't see such a
22 list.
23 Who were you assuming -- where do you see
24 that?

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1 A. I just see -- I'm just reading what they
2 stated here, and that they say they included in that
3 group of possibly contaminated those who contained an
4 active pharmaceutical ingredient from both -- both from
5 ZHP and from other companies.
6 Q. That's the -- all right. We're going in
7 circles and circles here, and I think we're really
8 struggling through something that should be really
9 simple.
10 This says at the bottom left-hand corner
11 of the second page that they identified those that
12 were, quote/unquote, probably contaminated with NDMA,
13 and then 36 additional products possibly contaminated
14 with NDMA, as they contained an active ingredient,
15 active pharmaceutical ingredient, both from ZHP and
16 from other companies.
17 A. Right. Yes.
18 Q. So that would be someone like a Teva that
19 was using ZHP's API and selling the product; right?
20 MR. INSOGNA: Object to form.
21 BY MR. SLATER:
22 Q. Or do you not know?
23 A. I don't know that.
24 Q. The other side of the study would not have

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1 been people who took ZHP valsartan at all; right?

2 A. Yes. I --

3 Q. Do you know which manufacturers are

4 included in that other side of the study? Does it say?

5 Because I don't see it.

6 A. It doesn't say.

7 Q. Did they analyze whether or not those

8 other manufacturers were also selling valsartan

9 contaminated with NDMA?

10 MR. INSOGNA: Object to form.

11 BY MR. SLATER:

12 Q. I don't see that either.

13 A. I don't see that on this particular

14 paper either, no.

15 Q. In fact, it's possible that people on

16 the -- what you termed the never side were taking pills

17 contaminated with NDMA also? That's possible as well

18 to some extent; right?

19 MR. INSOGNA: Form.

20 BY MR. SLATER:

21 Q. Because we know manufacturers other than

22 ZHP were also manufacturing and selling contaminated

23 valsartan in Europe at that time; right?

24 MR. INSOGNA: Object to form.

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1 A. I don't know the answer to that. It's

2 possible if they didn't exclude them and they didn't

3 know about it at the time, because this publication was

4 in 2018 as opposed to the Gomm study which was later in

5 2021.

6 BY MR. SLATER:

7 Q. Well, did they talk about excluding any

8 other manufacturers or identifying other manufacturers

9 as having contaminated pills, or do they link only to

10 ZHP here explicitly?

11 A. Looks like just to ZHP here.

12 Q. For example, in the never group, do you

13 know when Torrent announced their contamination of

14 their pills?

15 MR. INSOGNA: Object to form.

16 A. The date?

17 BY MR. SLATER:

18 Q. Yeah. Do you know if -- I'll ask it

19 differently.

20 Do you know if Torrent announced their

21 contamination before or after this study was published?

22 A. I don't know.

23 Q. I'm going to -- I'd like you to assume for

24 purposes of this question that Torrent announced after

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1 the study was published that their pills were

2 contaminated with NDMA. Okay? I'd just ask you to

3 assume that.

4 A. That I'm assuming what? That it was done

5 before?

6 Q. After.

7 A. They presented after the study --

8 Q. Let me ask it again.

9 I'd like you to assume that Torrent

10 announced that its pills were contaminated with NDMA

11 after this study was published.

12 A. That makes sense.

13 Q. Do you know whether Torrent's pills were

14 contaminated?

15 A. There was -- yes, I think that's one on

16 the list.

17 Q. In fact, Torrent was buying its valsartan

18 API from ZHP.

19 Were you aware of that?

20 A. I think so, yes.

21 Q. And therefore, Torrent would have some of

22 the highest levels of NDMA that we would see in this

23 litigation, because it came from ZHP; right?

24 MR. INSOGNA: Object to form.

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1 A. Yes, and if they didn't account for that

2 as being from ZHP, I don't know. It doesn't say in

3 this paper.

4 BY MR. SLATER:

5 Q. So therefore, Torrent, since there was no

6 announcement or knowledge that Torrent had contaminated

7 valsartan, people who took Torrent valsartan would have

8 ended up in the never group, based on this description

9 of the study; right?

10 MR. INSOGNA: Object to form.

11 A. With that hypothesis, in that scenario,

12 that if there were drugs that came out later after the

13 study was done that ended up having also contaminants,

14 and it wasn't already accounted for, then yes, they

15 could have ended up in the control group of this

16 particular study.

17 BY MR. SLATER:

18 Q. And that would be problematic in terms of

19 the validity of the final results if you had highly

20 contaminated valsartan being taken by people in the

21 never group; right?

22 MR. INSOGNA: Form.

23 A. The results would be about ZHP compared to

24 other compounds would hold and that there's no

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1 difference in terms of their added risk, how I assess
 2 that.

3 MR. SLATER: Wait. Could I have that
 4 answer read back? I lost that.

5 [The requested portion of the transcript
 6 was read by the reporter.]

7 BY MR. SLATER:

8 Q. I don't think I understand.
 9 If people who took Torrent valsartan that
 10 was contaminated with NDMA were included in the never
 11 group, that would be problematic in terms of the
 12 results of the study, in terms of comparing the two
 13 groups; right?

14 MR. INSOGNA: Object to form.

15 A. In that hypothetical scenario, which was
 16 not specified here that that's actually what happened,
 17 then if there were drugs in the control arm that had
 18 contaminant that wasn't accounted for, then that would
 19 be problematic in terms of the assessment being done,
 20 and it would bias towards the null.

21 BY MR. SLATER:

22 Q. What about Hetero? Do you know if Hetero
 23 was in the contaminated side of the group or the never
 24 group, in terms of people who took Hetero valsartan?

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1 Do you know where they got grouped?

2 A. It seems like all the non-ZHP drugs would
 3 be grouped in the never.

4 Q. And we know that the Hetero valsartan was
 5 contaminated as well; correct?

6 A. Some lots.

7 Q. So that would be yet another point of
 8 uncertainty, where did the Hetero people end up and
 9 what was their level of contamination that they took;
 10 right?

11 MR. INSOGNA: Object to form.

12 A. In that scenario, if that was the case,
 13 yes.

14 BY MR. SLATER:

15 Q. Does this study grapple with this issue
 16 that we're talking about at all? Like do they analyze
 17 at all other manufacturers, how they determine whether
 18 other manufacturer's pills were contaminated?

19 Do they go into any of that at all?

20 A. They didn't, and the publication date of
 21 this is in 2018, like I mentioned. And so it may be,
 22 as I think you pointed out, that at the time that they
 23 were doing this study that it wasn't known.

24 Q. Did you ever look into determining --

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1 MR. SLATER: Whoa. Whoa. Rosemarie, your
 2 phone just came on off of mute. You might want to put
 3 it back on mute. Thank you.

4 BY MR. SLATER:

5 Q. Did you ever make any effort to determine
 6 which manufacturer's valsartan was recalled in Europe
 7 after the Pottgard study?

8 Did you look into that?

9 A. I looked at the dates at which all of the
 10 different recalls were being done over the time after
 11 the initial one on the FDA website I saw. They have a
 12 similar website, the EMA.

13 Q. You would agree with me, based on the
 14 questioning that we've been going through for the last
 15 several minutes, that that would be something that
 16 would be very important to consider and understand;
 17 right?

18 MR. INSOGNA: Object to form.

19 A. It would be important to understand. In
 20 the end, though, when I was asked to opine on whether
 21 or not these trace levels in these drugs were
 22 associated with known risks for cancer based on the
 23 data, this was one of the studies, and it does not show
 24 that there is evidence of an association.

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1 BY MR. SLATER:

2 Q. This study draws conclusions based upon a
 3 comparison of two groups of people, and based on an
 4 assumption that one group was probably or possibly
 5 exposed to contaminated valsartan and the other group
 6 was not?

7 That's where the data comes from, the
 8 comparison of the two groups; right?

9 A. Right.

10 Q. It's the base assumptions as to whether or
 11 not the people in the groups were exposed or not
 12 exposed to contaminated NDMA are not accurate, that
 13 would undercut the data completely; right?

14 MR. INSOGNA: Object to form.

15 A. But in that larger pool of patients
 16 getting the never, there are a number of companies that
 17 are not having the contaminant.

18 So even if there were -- after the fact
 19 that they learned that there were some companies that
 20 also did, then it would be a small subset of the whole
 21 of the nevers. It's not all of them, in other words.

22 So it's not enough to change the overall
 23 outcome per se until some dataset showed that. So in
 24 other words, it's an important point to consider, but

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1 it's not like that proves the alternative hypothesis in
 2 any way.
 3 BY MR. SLATER:
 4 Q. What it does, in fact, is presents an open
 5 question; correct?
 6 MR. INSOGNA: Object to form.
 7 A. An example of confounding, which is in a
 8 lot of association studies, that are despite all
 9 efforts, like in this case, it's an example of one that
 10 wasn't known to be adjusted for in the first place.
 11 BY MR. SLATER:
 12 Q. It's actually -- I don't mean to
 13 interrupt. I'm sorry.
 14 A. And it's a risk of all of these types of
 15 studies, but again, this is the study most closely
 16 related to our question, and even with that potential
 17 confounder, it's a small subset of the nevers.
 18 It's not all of them, in other words,
 19 whereas the ones that are classified in the known,
 20 probable, or possible, they are exposed. And so --
 21 Q. How can you make --
 22 A. -- two cohorts that are different.
 23 Q. How can you make that statement when you
 24 have absolutely no idea as to whether or to what extent

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1 the people in the never group were taking contaminated
 2 valsartan also?
 3 You don't have any idea how to quantify
 4 that, so you can't make the statement you just made;
 5 correct?
 6 MR. INSOGNA: Object to form.
 7 A. I'm stating that it's more likely than not
 8 not a large subset of that never group.
 9 BY MR. SLATER:
 10 Q. Well, what was the percentage of people in
 11 the never group that were taking contaminated
 12 valsartan?
 13 Do you have any idea?
 14 MR. INSOGNA: Object to form.
 15 A. Now that probably could be assessed,
 16 because you could go back and look at this. But in the
 17 meantime, I would assume that they would be a small
 18 subgroup, because there were many agents out there that
 19 weren't contaminated, and the chance that everyone in
 20 the control group, in other words, got a contaminated
 21 pill is essentially zero.
 22 BY MR. SLATER:
 23 Q. How many of the people in the control
 24 group were exposed to contaminated valsartan?

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1 You have no idea; right? There's no way
 2 for you to have any idea on that; right?
 3 MR. INSOGNA: Object to form.
 4 A. I estimate that it's likely a low amount.
 5 BY MR. SLATER:
 6 Q. You estimated -- you have no way -- that's
 7 a guess, there's no basis for you to make that
 8 statement other than to guess; right?
 9 MR. INSOGNA: Object to form.
 10 A. Based on probability, I would say that
 11 it's a low likelihood.
 12 BY MR. SLATER:
 13 Q. Probability of what? Probability of
 14 biased speculation? Which I think I just made up that
 15 term, which I think you can -- you can use if you want.
 16 But -- and let me, without kidding around -- I'm
 17 trying -- obviously not trying to be funny.
 18 But that sounds to me completely
 19 speculative, since you have absolutely no basis to know
 20 which manufacturers, what their contamination levels
 21 were, or how many took the pills from those
 22 manufacturers.
 23 You don't have any of that data; right?
 24 MR. INSOGNA: Objection. Argumentative.

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1 A. What I'm stating is that it's unlikely to
 2 be a large proportion of that group.
 3 BY MR. SLATER:
 4 Q. Based on what?
 5 A. Chance.
 6 Q. So you're just speculating?
 7 MR. INSOGNA: Object to form.
 8 A. You asked me to make an assessment of the
 9 quantity of patients.
 10 BY MR. SLATER:
 11 Q. What I think you said before is you could
 12 go do a follow-up study now. So in that context, my
 13 question is this.
 14 As we look at Pottegard, there's a
 15 significant open question as to who on each side of the
 16 study took contaminated valsartan and to what extent,
 17 and you would need to do a subsequent follow-up study
 18 and reanalyze the data in order to get any sort of
 19 reasonable degree of medical certainty as to the answer
 20 to that question; correct?
 21 MR. INSOGNA: Object to form. Compound,
 22 argumentative.
 23 THE WITNESS: To be more precise, you
 24 would need the actual data, yes.

<p style="text-align: right;">Page 274</p> <p>1 MR. INSOGNA: Adam, are you moving off of</p> <p>2 Pottegard now? We've been about an hour-and-a-half.</p> <p>3 MR. SLATER: I was thinking about moving</p> <p>4 off of Pottegard, although I like saying Pottegard a</p> <p>5 lot. But -- so we can go off the record.</p> <p>6 THE REPORTER: All right. One moment.</p> <p>7 THE VIDEOGRAPHER: We are going off the</p> <p>8 record at 4:44 PM.</p> <p>9 [A brief recess was taken.]</p> <p>10 [Deposition adjourned until</p> <p>11 the following day.]</p> <p>12</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p>	<p style="text-align: right;">Page 276</p> <p>1</p> <p>2</p> <p>3 I, DANIEL CATENACCI, M.D., the witness</p> <p>4 herein, having read the foregoing testimony of the</p> <p>5 pages of this deposition, do hereby certify it to be a</p> <p>6 true and correct transcript, subject to the</p> <p>7 corrections, if any, shown on the attached page.</p> <p>8</p> <p>9</p> <p>10</p> <p>11</p> <p>12 _____</p> <p>13 DANIEL CATENACCI, M.D.</p> <p>14</p> <p>15 Sworn and subscribed to before me,</p> <p>16 This _____ day of _____, 202_.</p> <p>17</p> <p>18</p> <p>19 _____</p> <p>20 Notary Public</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p>
<p style="text-align: right;">Page 275</p> <p>1 CERTIFICATE</p> <p>2</p> <p>3 I, JOHN ARNDT, a Certified Shorthand</p> <p>4 Reporter and Certified Court Reporter, do hereby</p> <p>5 certify that prior to the commencement of the</p> <p>6 examination, DANIEL CATENACCI, M.D., was sworn by me</p> <p>7 via videoconference to testify the truth, the whole</p> <p>8 truth and nothing but the truth.</p> <p>9 I DO FURTHER CERTIFY that the foregoing is a</p> <p>10 true and accurate transcript of the proceedings as</p> <p>11 taken stenographically by and before me at the time,</p> <p>12 place and on the date hereinbefore set forth.</p> <p>13 I DO FURTHER CERTIFY that I am neither a</p> <p>14 relative nor employee nor attorney nor counsel of any</p> <p>15 of the parties to this action, and that I am neither a</p> <p>16 relative nor employee of such attorney or counsel, and</p> <p>17 that I am not financially interested in this action.</p> <p>18</p> <p>19</p> <p>20 _____</p> <p>21 JOHN ARNDT, CSR, CCR, RDR, CRR</p> <p>22 CSR No. 084-004605</p> <p>23 CCR No. 1186</p> <p>24</p>	<p style="text-align: right;">Page 277</p> <p>1</p> <p>2 DEPOSITION ERRATA SHEET</p> <p>3</p> <p>4 Page No.____Line No.____Change to:_____</p> <p>5 _____</p> <p>6 Reason for change:_____</p> <p>7 Page No.____Line No.____Change to:_____</p> <p>8 _____</p> <p>9 Reason for change:_____</p> <p>10 Page No.____Line No.____Change to:_____</p> <p>11 _____</p> <p>12 Reason for change:_____</p> <p>13 Page No.____Line No.____Change to:_____</p> <p>14 _____</p> <p>15 Reason for change:_____</p> <p>16 Page No.____Line No.____Change to:_____</p> <p>17 _____</p> <p>18 Reason for change:_____</p> <p>19 Page No.____Line No.____Change to:_____</p> <p>20 _____</p> <p>21 Reason for change:_____</p> <p>22</p> <p>23 SIGNATURE:_____DATE:_____</p> <p>24 DANIEL CATENACCI, M.D.</p>

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Exhibit B



**THE UNIVERSITY OF CHICAGO
THE PRITZKER SCHOOL OF MEDICINE**

August 27, 2021

Daniel Catenacci, M.D.
Associate Professor of Medicine,
Department of Medicine
Section of Hematology/Oncology
Director, Interdisciplinary GI Oncology
Program
Assistant Director, Translational Research
University of Chicago Cancer Center
University of Chicago Medical Center
5841 S. Maryland Avenue, MC2115,
Chicago, IL 60637-1470
Phone: 773-702-7596 Fax: 773-834-9268
dcatenac@medicine.bsd.uchicago.edu
www.uchicago.edu

Re: Valsartan Litigation

Dear Counsel,

Please find a report regarding my opinions on this case below.

EXHIBIT

7

exhibitsticker.com

1. Biography/Qualifications

I am a physician, duly licensed to practice medicine in the State of Illinois. I have completed a Bachelor of Science in Biochemistry and a Doctor of Medicine, and then completed medical training in Internal Medicine residency and a Hematology & Oncology fellowship. I have also completed a Master of Science in Health Studies (Biostatistics, Clinical and Translational Investigation). I am Board Certified in Medical Oncology and practice clinically in the field of Medical Oncology with a subspecialty in Gastrointestinal Oncology, including treating patients with gastroesophageal, pancreatic, hepatobiliary (liver and bile duct), neuroendocrine, and small and large bowel cancers. I have been involved in these patients' care including various therapies in the perioperative curative-intent as well palliative metastatic settings. I conduct research in these same tumor types from both clinical and basic research perspectives.

At the University of Chicago, I am the Director of Gastrointestinal (GI) Medical Oncology Program. This entails overseeing a clinical program that includes 6 GI Medical Oncology Faculty members, 3 Advanced Nurse Practitioners, 6 nurse navigators, and a Pharmacist, as it pertains to operations of the clinical and research programs within GI Medical Oncology. Annually, we have a census of > 1600 GI cancer patients, of which >350 are new patient and new consultation visits. In addition, I oversee and run the research program that includes 4 clinical trial coordinators, 4 data managers, regulatory personnel, and biobank personnel. The GI research program has more than 30 investigational clinical trials open at the moment. This extends to 3 community satellite centers of the University of Chicago where our studies are available. As the Director of Interdisciplinary GI Oncology and Assistant Director of Translational Research, this research focus extends to the other oncologic disciplines of GI Surgical Oncology, Radiation Oncology, as well as Anatomical and Molecular Pathology, where I oversee and facilitate cross-discipline collaboration and research.

I have authored numerous publications focusing on the management of GI and other cancers, as well as biologic mechanisms of cancer growth, novel therapeutics, and mechanisms of therapeutic resistance of these diseases. I have presented these topics and my research findings internationally at medical conferences and by invitation to academic centers. I have obtained NIH/NCI research funding, foundation awards, collaboration with biotech and pharmaceutical companies, and philanthropy to support my work. A primary research focus of mine is on the biological understanding and treatment of gastroesophageal (esophagus, gastroesophageal junction, and stomach) cancers, by studying the normal and oncologic components and molecular pathways of gastrointestinal cells. My research agenda has an overarching goal to validate and improve personalized treatment, immunotherapy, and precision medicine for gastroesophageal cancer and other GI cancers, with findings often relevant to all cancers. A major component of my research is on the quantification of tumor genetic molecular heterogeneity both between individuals with gastroesophageal cancer, but importantly also within a given individual within one tumor site, and from one tumor site to another, and how this impacts personalized targeted therapeutic approaches. To overcome many biological hurdles of the disease that has led to failed therapeutic approaches in the past 1-2 decades, I have designed and executed novel clinical trials to implement treatment strategies based on these laboratory and clinical discoveries.

I serve as a mentor to medical trainees including medical students, internal medicine and surgical residents, as well as medical oncology and surgical oncology fellowship trainees. Most teaching is part of clinical training during clinical care of patients in the inpatient and outpatient setting. I also teach formal didactic lectures to these trainees on the topics of management of various GI cancers. I also teach didactic lectures to first and third year Graduate Students in Cancer Biology regarding the biologic underpinnings of GI cancer and therapeutic strategies.

I serve as associate editor for the Journal of American Medical Association Network Open (JAMA Netw Open), and I am also on the editorial boards of the Journal of Clinical Oncology Precision Oncology (J Clin Oncol PO), the journal Cancer, and the journal Cancers. As associate editor for the Oncology section of JAMA Netw Open, I review manuscript submissions pertaining to all cancers and from all disciplines (medical, surgical, and radiation oncology) to the journal and determine which manuscripts will be sent for external peer review versus those that would be rejected without review. I then review those manuscripts and external peer reviewer comments and provide a final decision as to whether to reject or accept the paper for publication. As associate editor of JAMA Netw Open and member of the editorial boards of J Clin Oncol PO, Cancer, and Cancers, I attend regular board meetings to discuss papers and general operations of the journals. I also serve as an ad hoc reviewer for numerous journals to serve as an external peer reviewer to provide comments and recommendations on acceptance of manuscripts, pertaining to GI cancers, submitted for publication.

I am a member of many medical societies and groups, including the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), and the American Association of Cancer Research (AACR). I have participated in consensus guidelines for the treatment of GI cancers for ASCO and other Consortia.

A copy of my curriculum vitae is attached as Exhibit A.

2. Scope and Summary of Opinions

I have been asked to describe cancer in general terms, and the ways in which cancer develops in humans (cancer pathogenesis or carcinogenesis). More specifically, I have been asked to describe a) aerodigestive cancers, including gastrointestinal (GI) cancers (esophageal, gastric, pancreatic, liver and colorectal/intestinal cancers), lung and pharyngeal cancers, genitourinary (GU) cancers (bladder, kidney, prostate, and uterine cancers), breast cancers, and hematologic (blood) malignancies; b) known causes and risk factors that are associated with these cancers, their general carcinogenesis timeline, and their overall incidences annually; and c) surveillance strategies and rationale as it pertains to primary and secondary screening interventions for each of these cancers.

In addition, I have been asked to evaluate the question of whether there is reliable scientific evidence, including consideration of epidemiologic, toxicological, and animal data, that the antihypertensive valsartan containing drugs (VCDs) (or other angiotensin receptor II blockers (ARBs) like losartan, irbesartan, and others) and in particular VCDs identified to have trace levels of the impurities N-nitrosodimethylamine (NDMA) and/or N-Nitrosodiethylamine (NDEA), are associated with or cause cancer of any type. My report focuses on NDMA as this

is the area with the most available data regarding these questions, but my interpretation and conclusions of these data generally pertain to NDEA as well.

Methods/Materials Reviewed:

This report is offered pursuant to Rule 26 of the Federal Rules of Civil Procedure. Each of the opinions I have offered in this report is given to a reasonable degree of medical probability and/or certainty, and is based on the same methodology I routinely use in my professional life as an active cancer researcher and scientific journal editor, reviewer, and publisher. I reviewed and analyzed the available medical and scientific literature on these subjects, in particular, literature pertaining to the risk factors for cancer, background rates and risks of certain cancers in the general public and in hypertensive patients, the (lack of) association between angiotensin II receptor blockers (particularly valsartan) and cancer, and literature concerning NDMA/NDEA/nitrosamines and cancer/carcinogenesis. The facts and data set forth in this report are the types of facts and data on which I rely in my clinical research and on which other oncology researchers reasonably rely. In addition, I applied my education training and experience in cancer to my analysis of those facts and data. I have done (and continue to do) independent reading and literature searches pertaining to the topics above, including PubMed among other sources.

Summary of Opinions Offered

A more detailed explanation of my opinions are contained in the body of the report below. A brief summary of the major conclusions of my analysis follow:

- Cancer is not a monolithic disease but rather a collection of different diseases which have in common the uncontrolled and deleterious growth of cells in the body. Moreover, even within the broader categories, for example, of GI or GU cancers, as well as within any particular type of GI/GU cancer or other listed cancer of interest (lung, pharyngeal, breast or blood), there are important differences in terms of cancer biology, pathogenesis, risk factors, and effective treatments.
- Cancer has, at its core, a genetic etiology, often the result of inheritance (a non-modifiable risk) but more commonly a result of somatic alterations that can occur any time after conception and after birth. Some of the possible causes and risk factors contributing to non-inherited cancer (potentially modifiable risks) can be environmental, such as the common examples of prolonged exposure to tobacco smoke, asbestos, or the harmful prolonged radiation of the sun. In most cases, however, the actual cause of a particular cancer cannot be definitively determined.
- Cancer development generally takes several years and often many decades to fully develop, depending on the type of cancer and the etiology of that cancer.
- As an initial step in an analysis whether an external exposure causes any type of cancer, the human epidemiological data must establish a valid association. Even a valid epidemiological association, however, does not establish causation. To support a causal conclusion, epidemiological evidence must be well-designed and

well-conducted, statistically significant, replicated, and consistent to a reasonable degree across independent studies, among many other well-recognized criteria.¹ In the case of VCDs, upon my review it is my opinion that such evidence does not support the conclusion that VCDs in general, nor the VCDs identified to have trace levels of an NDMA and/or NDEA impurity, are associated with nor causative of any particular cancer, including any particular GI or GU cancer, nor lung, pharyngeal, breast, or blood cancer.

- While animal data and dietary data can contribute to the basis upon which to conclude that an exposure causes a particular outcome, in the case of VCDs identified to have trace levels of an NDMA impurity, the available data provides no such evidence that it is carcinogenic in humans at the exposure level and duration of these VCDs during the less than 4 years of potential exposure from late 2014 to the mid-summer of 2018.
- Data pertaining to NDMA/NDEA do not permit the conclusion that VCDs containing trace amounts of those impurities cause cancer. While there is much controversy in the medical and scientific communities about nitrosamines generally, and NDMA in particular, regarding whether exposure to such molecules increases the risk of any cancer in humans, the data are, at best, inconclusive. Moreover, since dose, duration of exposure, and pharmacokinetic issues including DNA repair are important considerations to understand whether a drug or chemical represents an increased cancer risk, that there may be some trace level of NDMA in certain formulations of VCDs cannot alone demonstrate that there is an increased risk of any type of cancer associated with exposure to those medications.
- The United States Preventive Services Task Force (USPSTF) publishes recommendations on whether to screen asymptomatic individuals for a given cancer, and under which scenarios this screening is or is not appropriate, or when there is insufficient data (for which the recommendation is not to do so). Other than a few cancer types (colorectal, breast, cervical cancers meeting age criterion, along with prostate and lung cancers and colorectal cancers at younger age that meet certain limited criteria) there are no generally accepted recommendations to actively screen asymptomatic patients for any other cancer. There are no specific indications to screen individuals any differently for those patients who are known to have taken VCDs identified to have trace levels of an NDMA or NDEA impurity.
- After consideration of the totality of available data, the scientific evidence does not support the conclusion that VCDs, and particularly the VCDs identified to have trace levels of an NDMA impurity, are associated with or cause any form of cancer (including the stated GI, GU, lung, pharyngeal, breast, or blood cancers) in humans at the exposure levels relevant for this litigation. Moreover, there is insufficient evidence that patients known to have been exposed to any VCD identified to have trace levels of an NDMA or NDEA impurity should undergo any surveillance outside the regular recommended surveillance for any given cancer type.

All of the opinions expressed in this report are held to a reasonable degree of medical and scientific certainty. In forming my opinions, I have relied on my training, expertise, and experience, as well as my review and consideration of the literature and other documents referenced in my report and/or listed in Exhibit B, including expert reports submitted by plaintiffs, and the sources cited therein. Citations to specific sources are offered as endnotes in the text of this report, where I believed it necessary to reference a specific source; otherwise, my opinions draw on a combination of the reference sources listed in Exhibit B, my own clinical experience, and my general medical training, knowledge, and ongoing review of medical and scientific literature. Exhibit B is not intended to be an exhaustive list of all source materials I considered or knowledge I had available to me in forming these opinions.

This report is not intended to set forth every opinion that I might have or develop in this litigation, and I reserve the right to supplement my list of source materials and/or to amend or supplement these opinions if additional information becomes available. I also reserve the right to respond to and rebut any information, testimony, or document(s) produced during discovery, which I understand is ongoing, and to respond to any opinions offered by Plaintiffs' experts at their depositions or at trial. Further, as requested by counsel this report contains my opinions regarding general causation only. It does not contain case-specific opinions or opinions concerning the cause of any specific plaintiff's cancer, liability, damages, or other defenses, which opinions I reserve the right to offer at a later time and through a subsequent report.

Attached as Exhibit C is a fee schedule, which sets forth my customary hourly rate for expert witness services, which is applicable to my work in this litigation.

Attached as Exhibit D is a list of cases in which I have previously given expert testimony in the past four years.

3. Introduction to Cancer

Cancer is the abnormal and uncontrolled growth of cells in the body.² Cancer cells are a distorted version of a normal cell – it is well-established that cancer arises from alteration of one or more cancer-related genes due to change of the DNA sequence and/or changes in the amount of DNA (amplification/deletion), or the expression of the gene itself (through epigenetic changes).

Cancer-related genes can be one of two main categories: tumor suppressor genes or oncogenes. Tumor suppressor genes are the 'brakes' in the system, and signal for cells to stop dividing/growing; if there is severe damage to the cell, they signal for it to die (apoptosis or senescence).³ Oncogenes are the 'gas pedal' of the system, signaling for cells to divide, increase in number, and grow in size, and also some oncogenes signal the cell to migrate to other areas in the body.² Normally, tumor suppressors and oncogenes signal in concert and in equilibrium with each other to maintain a balance, called homeostasis. If there is a wound, nearby cells will be signaled to divide, grow, and migrate to the wound to heal it, but when healed, the cells will return to steady-state. Cancer cells signal to grow inappropriately, due to altered DNA, and behave like a wound that never stops healing.⁴ Cancer cells continue to grow inappropriately and the ratio of cell growth to cell death increases, and therefore often cancer masses will form, referred to as 'tumors'. However, some tumors grow as single invasive cells

in the absence of classic tumor formation, called diffuse type tumors, such as signet ring gastric cancers.

Although different cancers from different sites and tissues of the body have different sets of altered genes causing the cancer, ultimately, all cancers are caused by alterations in DNA.⁵ However, not all alterations in the genes are pathogenic (i.e. the alterations must inactivate tumor suppressors or active oncogenes inappropriately in order to be pathogenic; if they do not, they are considered ‘passenger’ mutations without function). Moreover, even pathogenic alterations can be ‘fixed’ by DNA repair. It is only those pathogenic alterations of the DNA that remain ‘unrepaired’ within cancer-related genes that are problematic, and these DNA alterations may be either inherited, induced by environmental factors, from random DNA replication errors, or a combination of these factors. A carcinogenesis model has been described for various cancers specifying common genes altered and the sequence in which this occurs over a period of several years.⁵ It has been estimated that at least half of the genetic changes occur in precursor cancer cells prior to formation of any tumor mass.⁶

Inherited pathogenic alterations, called germline alterations, can be from a single highly penetrant gene (e.g. a tumor suppressor like the APC gene in colorectal cancer),^{7,8} or they can be weaker penetrance and also can be multifactorial (multiple causative genes, but each contributing to the develop of cancer to a small degree) and more difficult to discern. A germline event(s) is present prior to the formation of the zygote (the one cell made up of DNA that is half from one parent and half from another parent, also known as a fertilized egg) in the DNA of one (or both) parents. It is estimated that inherited genetic factors are causative or contributory to approximately 5-15% of cancers, depending on the cancer type. Inheriting an altered pathogenic gene usually leads to the onset of a cancer at a younger age, due to the carcinogenesis model shifting earlier in time (i.e. the cancer development gets a ‘head start’ right from development).

On the other hand, somatic alterations are those that occur after conception of a zygote, through gestational development, and then after birth and through an individual’s lifetime.^{6,9,10} Somatic genetic alterations can occur from environmental exposures and/or from random DNA replication errors, also referred to as stochastic effects associated with the lifetime number of stem cell divisions within each tissue.¹⁰ In other words, this is why cancer is overwhelmingly a disease of older persons — as cells continue to divide over an individual’s lifetime, there are more opportunities for random mutations to occur and accumulate, which accumulation ultimately could lead to cancer. Reports have estimated that stochastic random genetic alteration over time can account for up to two thirds of cancers. In other words, the lifetime risk of cancers of many different types is strongly correlated (0.81) with the total number of divisions of the normal self-renewing cells maintaining that tissue’s homeostasis; this is why cancer is generally associated with older age.⁹ These results suggest that only approximately one third of the variation in cancer risk among tissues is attributable to environmental factors or inherited predispositions.

Environmental factors that contribute to the cause of cancer have been described, and can be specific to certain cancer types.¹¹ Environmental factors include aspects of lifestyle, economic, and behavioral exposures. Poor diet,^{12,13,14} inactivity and sedentary lifestyle,^{15,16,17,18} and

obesity^{19,20} and metabolic syndrome¹⁴ have each been associated with carcinogenesis. Some specific foods are linked to specific cancers.²¹

Importantly, hypertension has been associated with increased cancer risk and cancer mortality, particularly as it also tracks and closely associates with other cancer-related risk factors of smoking, alcohol use, obesity, diabetes, diet, and other factors. After adjusting for these known cancer risk factors, however, hypertension is also potentially an independent cancer risk factor in a number of tumor types including renal (kidney), colorectal, breast, esophageal, liver, and uterine cancers.^{22,23,24}

Broadly speaking, any factor that may alter one's DNA sequence could contribute to carcinogenesis and the ultimate development of cancer and can be referred to as a carcinogen.²⁵ Mutagens are substances or agents that cause DNA changes, and carcinogens are mutagens that promote DNA changes leading to cancer. Mutagens that merely cause changes to the DNA which ultimately do not lead to the development of cancer are not carcinogens. Tobacco smoke, for example, is common and well-known to contain over fifty carcinogens, including hydrocarbons.²⁶ In addition to chemicals, radiation and radioisotopes are carcinogens.²⁷ Infections with certain viruses, bacteria, and worms are also known carcinogens.^{28,29} Endogenous or exogenous hormones drive cell growth and are also known carcinogens. Importantly, however, human cells are continually bombarded with agents that can alter DNA, without leading to cancer. In some cases, no mutation occurs, despite exposure to a mutagen; in other cases, mutations do occur, but do not lead to cancer. Many mutations impact non-coding DNA and have no impact on cancer development; other mutations are corrected by cellular mechanisms before the cell divides, preventing carcinogenesis.

The International Agency for Research on Cancer (IARC) has listed groups of agents into categories (Group 1, 2A, 2B, 3, 4) as follows, based on the strength of available evidence supporting designating as a human carcinogen²⁹:

Group 1: the agent (mixture) is definitely carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans.

Group 2A: the agent (mixture) is probably (product more likely to be) carcinogenic to humans. The exposure circumstance entails exposures that are probably carcinogenic to humans.

Group 2B: the agent (mixture) is possibly (chance of product being) carcinogenic to humans. The exposure circumstance entails exposures that are possibly carcinogenic to humans.

Group 3: the agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity to humans.

Group 4: the agent (mixture) is probably not carcinogenic to humans.

Cancers are classified by the cell type of origin.³⁰ The most common cancers are carcinomas, those derived from epithelial cells, such as the mucosal lining of the GI tract. Sarcomas are

another group of cancers that arise from the connective tissue like muscle, bone, and cartilage with precursor cells called mesenchymal cells. Malignant hematopoietic cells (leukemia and lymphoma) arise from blood-forming cells in the bone marrow and or lymph tissue in the body. Other less common cell types of origin are germ cell tumors (derived from pluripotent stem cells and in tissues such as testicle and ovary), or blastomas (cancers derived from immature precursor cells or embryonic tissue).

The normal cell cycle and behaviors of each of these tissues (regular death, senescence, and/or sloughing/loss of differentiated cells in the tissue) generally would not allow enough time for the accumulation of the necessary changes that lead to carcinogenesis. Accordingly, it is generally presumed that the resident stem cells in each tissue type (which are present longer term) are the cells of origin for the cancer type(s) arising in those tissues. It takes time for the accumulation of all the genetic and epigenetic and stromal changes required for the emergence of a neoplastic (i.e. “cancerous”) cell. The time required — which we have learned from years of research and modeling — accounts for the significant latency period of the carcinogenesis models of cancers in each of these tissues.^{9,10,31,32}

4. Cancer Prevention, Screening, and Incidence

The incidence of cancer (all) has slightly increased for people of all ages over the last decades. In 1975, neoplasms for those less than age 65 accounted for 22% of deaths in United States, compared to 23% in 2018, the latest year for which these data are available. In those aged over 65 years, cancers caused 18% of deaths in 1975, compared to 25% in 2018. That is, one in every four deaths are due to cancer. The incidence of new cancer cases in the United States in 2018, was 1,708,921, and 599,265 people died of cancer. In one year (2018), for every 100,000 people, 436 new cancer cases were reported (4.36/1000 people) and 149 people for every 100,000 people (1.49/1000 people) died of cancer. As such, cancer is the second leading cause of death in the United States, exceeded only by heart disease (655,341 deaths in 2018). In 2020, an estimated 1,806,590 new cases of cancer will be diagnosed in the United States and 606,520 people will die from the disease.^{33,34}

Cancer prevention and screening measures can decrease the incidence and mortality of some cancers.³⁵ Controllable lifestyle choices (avoiding smoking, inactivity, high fat diet, etc.) and avoiding known carcinogens such as radiation can help to prevent carcinogenesis – these are modifiable risk factors of cancers. This is in contrast to unmodifiable risk factors such as gender and/or age.

Because there is a latency to the development of outright invasive cancer through various stages of preneoplastic and neoplastic progression, specific screening using specific diagnostic efforts in some circumstances, such as general screening of the public for certain cancers has been implemented.^{36,37} This screening has been recommended by professional medical organizations due to relatively high incidences of these cancers coupled with demonstration of improved survival in these select (relatively few) cancer types. However, most cancers do not have routine screening recommendations to date. This screening is referred to as primary screening (screening done in the public for those who have not previously had a cancer). The screening recommendations are graded by the United States Preventive Services Task Force (USPSTF) based on the strength of the evidence and the certainty level of benefit as follows:³⁸

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

The following are particular general primary screening interventions of the American public which have been shown to be able to identify early preneoplastic or early stage cancers that can be treated, with consequent improvement in overall survival in these specific cancers compared to no screening, and given their incidences and risks in the American population:

- colonoscopies for colorectal cancer (age ≥ 50 USPSTF Grade A; age 45-49 Grade B; age 76- 85 USPSTF Grade C),^{39,40}

- mammograms for breast cancer (age 50-74 USPSTF Grade B; age 40-49 USPSTF Grade C; Age ≥ 75 USPSTF Grade I),^{41,42}
- PSA testing for prostate cancer (potentially between the ages of 55-69, with USPSTF Grade C, but Grade D for ages ≥ 70),^{43,44}
- Pap smears for cervical cancer (ages of 21-65 with USPSTF Grade A, while <21 or >65 Grade D).⁴⁵

Importantly, in addition to the above, there are recommendations to NOT screen for the following specific cancers in asymptomatic adults: bladder, pancreatic, ovarian, thyroid, testicular cancers each having USPSTF Grade D recommendation. Skin cancer and oral/pharyngeal screening has a USPSTF Grade I recommendation.³⁸

There are a few recommended targeted screening programs for high risk individuals such as chest CT scans for current/previous heavy smokers for lung cancer (starting at the age of 55) and abdominal imaging of patients with cirrhotic livers for liver cancer. These specific targeted recommendations will be discussed below in each specific cancer subsection.

There are also a few select set of specific recommendations for higher risk individuals for some cancers to undergo primary screening at certain times. For example, genetic testing is recommended for specific high-risk individuals, as is identifying families and individuals harboring specific pathogenic germline (inherited) genetic events who then undergo intensive screening at earlier ages, which may improve early detection and treatment for these patients. In addition to carrying an abnormal gene since birth, other specific examples for the pertinent cancers where higher risk patients are recommended to be screened (and how) are discussed below in each specific subsection. Some examples which would put a patient at higher risk includes a patient who has a personal history of cancer or an illness that is known to predispose to cancer with high rate (eg inflammatory bowel syndrome). For patients who have already had a cancer, further screening in them is referred to as secondary prevention (to identify a potential second cancer earlier).

The reason for guidelines on cancer screening is that there are potential risks and negative consequences to screening including patient anxiety and false positives.^{32,35,36,37,38,39} There is no basis in the USPSTF screening recommendations for someone to subject themselves to enhanced screening for the types of cancers at issue in this litigation, given that there is lack of definitive evidence of increased cancer risk at the levels of NDMA found in VCDs, or that screening in this situation has any utility. The risks and negative consequences of cancer surveillance outside of what would already be recommended routinely is greater than any risk from NDMA. It is notable, however, that the vast majority of patients taking antihypertensive medications, including VCDs and VCDs with NDMA impurity, would be older and will already be receiving the routine recommended screening for the cancers noted above by the USPSTF guidelines.

5. Cancer Symptoms, Diagnosis, and Staging

Cancer is diagnosed, usually, with the presence of various symptoms that are a consequence of the primary site of origin of the cancer and/or from sites of metastatic spread.⁴⁶ Solid tumor cancers (of epithelial, mesenchymal, germ cell or blastoma origin, along with subgroups of lymphomas) often cause localized symptoms due to mass effect or involvement at the site of origin that are often specific to that site. This can include pain, discomfort, and/or negative effects on the function of the organ site of origin. Hematologic malignancies (referred as ‘liquid’ cancers) often cause cytoplasias (blood cell abnormalities) that lead to their dysfunction and consequent symptoms such as fatigue from anemia, bleeding from thrombocytopenia, and infection from white blood cell dysfunction or leukopenias. Cancers can also be identified through routine screening of high-risk or average risk patients through screening measures (when appropriate and recommended), in the absence of symptoms. Also, cancers can be identified incidentally when evaluating other unrelated issues.

Diagnostic tools include physical exam and vital signs, laboratory studies, and various imaging studies including ultrasounds (US), computerized tomography (CT scans), magnetic resonance imaging (MRI), and positron emission tomography (PET scans), and other specialized imaging procedures. A number of scoping procedures to visualize affected organs are also used, including endoscopies (GI from above, EGD; GI from below, colonoscopy), bronchoscopies, and cystoscopies. Sometimes surgical explorations are required including laparoscopies or video-assisted thoracoscopic surgeries (VATS). Ultimately, biopsies of affected tissue and evaluation under the microscope by a pathologist is generally used to arrive at the definitive diagnosis of cancer.

With the diagnostic tools above, cancers are staged to determine the extent of the disease throughout the body. Early stages (for solid tumors) are those that are confined to the site of origin. Locally advanced cancers are those that are confined to the site of origin but advanced to regional structures and lymph nodes around the site of origin. Advanced metastatic cancers are those that have spread to distance sites away from the site of origin. Cancers are staged because this determines the prognosis of the cancer and also the optimal treatment approaches. Generally, the higher the disease stage at diagnosis, the worse the overall prognosis.

6. Cancer Treatment

Treatments for cancer vary by cancer type, stage, and patient characteristics. Generally cancers of early stages have good prognoses with local therapies alone, including surgery and/or radiation. Cancers that are locally advanced often require ‘adjuvant’ (or ‘neoadjuvant’) systemic treatments like chemotherapy or immunotherapy in addition to the localized treatments, since they have a higher risk of having occult (undetected but present) micro-metastatic disease. Treatments such as chemotherapies, targeted therapies and immunotherapies can enhance the cure rates in these situations.

Cancers that are metastatic generally have relatively poor prognosis and, to date, are mostly incurable. In the metastatic setting (Stage IV), therapies including chemotherapies, targeted therapies and/or immunotherapies are palliative with intention to decrease/prevent cancer-related symptoms and improve survival time, but they are not curative. Different

chemotherapies, targeted therapies, and/or immunotherapies are used for different cancers and subtypes of cancers.

Ideal treatment for any given scenario is applied to a given patient's context. That is, if a patient has a poor performance status (unable to perform daily activities on their own without help) and multiple comorbidities (e.g. heart disease, uncontrolled blood pressure, neurologic dysfunction, liver dysfunction, low blood counts etc), then it is often not possible to provide ideal therapies due to these competing problems, and these patients tend to have worse prognosis overall as a consequence.

I also reviewed the expert report offered by Dr. Panigrahy in this litigation. In that report, Dr. Panigrahy obliquely comments that "continued exposure to NDMA and/or NDEA can... otherwise interfere with cancer therapy." (See Panigrahy Report, at p. 221). No citation is provided for that assertion and it is unclear what he intends to say; I am aware of no literature supporting that proposition. Neither exposure to NDMA/NDEA, nor exposure to VCDs potentially containing NDMA/NDEA is something I consider when deciding treatment options or recommending a specific course of treatment for any of my oncology clinic patients. I am unaware of any specific consequence that prior NDMA or NDEA exposure could have on the efficacy or tolerability of any cancer therapy or any literature that would support Dr. Panigrahy's theory.

7. Post-Treatment Cancer Surveillance

For patients with cancers that are treated with curative intent, surveillance is performed after completion of the prescribed therapy in order to identify a recurrence of the original cancer. Surveillance usually entails regular visits with the patient's provider every 3-6 months, along with laboratory and imaging tests periodically, in order to identify recurrences and to act upon them before they become symptomatic, sometimes with curative intent, and most often still with palliative intent. After 5-10 years of surveillance (depending on the cancer type and circumstances), the risk of recurrence usually decreases such that patients may be followed per routine with their general healthcare provider.

8. Specific Cancers of Interest

8a. Introduction to Gastrointestinal Cancers

In 2019, approximately 328,030 new cancers of the digestive system will be diagnosed in the United States, which makes it the most common physiologic system afflicted by cancer and more common than breast cancer (n = 271,270), lung and respiratory tract cancers (n = 246,440), and genitourinary cancers (n = 295,290). Approximately 165,460 patients will die annually of GI malignancies, including 51,020 patients with colorectal cancer, 45,750 patients with pancreatic cancer, 31,780 patients with liver and intrahepatic bile duct cancers, and 27,220 patients with gastroesophageal cancers (GECs).^{33,47,48} The incidences of these cancers in 2018 were as follows: colorectal cancer 141,074 (age adjusted rate 36.5/100000 people); pancreatic cancer 52,546 (age adjusted rate 13/100000 people); liver and bile duct 34,638 (age adjusted rate 8/100000 people); gastroesophageal cancers 42465 (age adjusted rate 11/100000 people).

The total incidence, then, for GI cancers in 2018 was 270,723 (age adjusted rate 68.5/100000 people).³⁴

The spectrum of diseases encountered in this field varies from rather indolent malignancies, such as low-grade neuroendocrine tumors with overall survival (OS) measured in years, to very aggressive and rapidly fatal cancers, such as pancreatic and hepatocellular carcinomas, for which, in advanced stages, survival is typically measured in months to a year. Several cancers of the digestive tract are linked to hereditary syndromes that require genetic counseling of patients and family members.

Introduction to Gastroesophageal Cancer (GEC):

GECs exhibit great variation in histology, geographic distribution, and incidence over time. Recent classification generally comprises three main gastroesophageal cancer subtypes, reflecting our current understanding of the anatomy, history, etiology and molecular basis of these cancers: (1) gastroesophageal junction (GEJ) or esophageal junction (EJ) adenocarcinomas; (2) esophageal squamous cell cancer (SCC); and (3) distal gastric AC.

Numerous histologic subtypes have been described, particularly pertinent to gastric AC but also for GEJ AC, including histologic differentiation (ie, well, moderate, poor), Lauren classification (ie, intestinal, diffuse, mixed type), presence of signet-ring cells or not, and a whole host of other subtypes in the WHO criteria.⁴⁹ Despite the noted differences between GEJ AC and gastric AC, these two subtypes are often grouped together as gastroesophageal adenocarcinoma (GEA) in both the locally advanced and metastatic settings, when considering therapy.^{50,51}

In the United States, GECs, together, represent the third most common GI cancer (after colorectal and pancreatic), with the third highest mortality rate.^{34,52} Worldwide, they are the third most common cancer and second leading cause of cancer mortality.⁴⁸ The risk factors for the various subgroups of GEC are quite different with esophageal SCC strongly associated with smoking and alcohol use, much like lung SCC and pharyngeal SCC. Historically, the most common types of GECs were esophageal SCC of the upper to middle esophagus and distal gastric AC.⁵³ However, during the past three to four decades, particularly in western countries, including the United States, the incidences of esophageal SCC and distal gastric AC have decreased. In contrast, the incidence of GEJ AC has reciprocally increased rapidly during this same period in the Western world, paralleling the rise of gastroesophageal reflux disease (GERD), obesity, diabetes, high fat diet, and metabolic syndrome in the general population. These cancers are also notably and significantly associated with patients with a high body mass index.^{54,55}

Esophagogastric Junction Adenocarcinoma

GEJ ACs typically arise in metaplastic epithelium—a condition known as Barrett esophagus (BE).⁵⁵ Murine carcinogenesis models suggest migration of precursor cells from the gastric cardia proximally into the distal esophagus.⁵⁶ The incidence of BE is 10% to 20% among symptomatic patients who undergo endoscopy and 30% to 50% for patients with peptic strictures. Risk factors associated with BE include GERD, white or Hispanic race, family risk,

male sex, advanced age, smoking, diabetes mellitus, Western diet, and obesity and metabolic syndrome.^{55,57,58} However, there is heterogeneity in carcinogenesis and not all tumors arise within a BE background. Approximately 60% of GEJ AC cases have evidence of precursor BE. In a nationwide population study from Denmark, the relative risk of AC among patients with BE was 11.3 (95% CI, 8.8 to 14.4) compared with the risk in the general population.⁵⁹ The annual risk of GEJ AC was 0.12% (95% CI, 0.09 to 0.15).

There is an inverse association between *Helicobacter pylori* infection and GEJ AC, potentially as a result of the reduced acidity associated with atrophic gastritis.⁶⁰ Whether rigorous medical management of GERD with long-term use of proton-pump inhibitors (PPIs) can affect the natural history of the disease or the development of malignancy has long been debated. A recent, large prevention study, ASPECT, evaluated this question in patients with BE ≥ 1 cm and no HGD or esophageal AC.⁶¹ A total of 2,563 patients were randomly assigned to high-dosage (40 mg twice daily) or low-dosage (20 mg once daily) esomeprazole PPI acid suppression, alone or combined with aspirin 300 mg/d. The primary composite end point was time to all-cause mortality, esophageal AC, or high-grade dysplasia. The combination of aspirin with high-dose PPI had the strongest effect, compared with low-dose PPI with no aspirin.⁶¹ Another recent, large, population-based retrospective analysis of Nordic countries evaluating 942,906 patients with GERD reported that medical and surgical treatments of GERD were associated with a similar reduced esophageal AC risk, with the risk decreasing to the same level as that in the background population over time, supporting the hypothesis that effective treatment of GERD might prevent esophageal AC.⁶² Other than antireflux medication⁶¹ and antireflux surgery,⁶² the typical treatment of patients with BE is surveillance using upper endoscopy and collecting a biopsy specimen to examine tissue for evidence of dysplasia.⁵⁷

Gastric AC

In the United States, gastric AC is seen twice as often in men as in women and more frequently in black men than in white men, and its incidence increases with age, starting at 50 years.⁶³ The incidence of gastric AC has varied considerably during the past century. In the United States, the incidence of gastric AC has decreased approximately 75% during the past few decades.⁵² Although gastric AC rates have declined worldwide, it is still prevalent in regions of the world where the storage of fresh foods and the quality of water are poor and in some industrialized nations as well (e.g., Japan).⁶⁴ Gastric AC is a major health issue in Japan and Korea, and both countries have nationwide screening programs. In Japan and Korea, gastric AC is associated with a better prognosis than in western cultures and thought to be multifactorial including different disease biology, different treatment approaches, and other unknown factors. When controlling for baseline tumor characteristics, patient demographics, and surgical factors, there is a difference in survival that remains unexplained.⁶⁵ Studies of migrant populations have supported evidence for the effect of environmental influences on the development of gastric AC.^{66,67} Factors associated with an increased risk of gastric AC include nutritional factors such as high salt and high fat diets, a diet low in vitamins A and C, the consumption of large amounts of smoked or cured foods, lack of refrigerated foods, and poor-quality drinking water.⁶⁸ Occupational exposure to rubber, asbestos and coal also increases the risk.^{75,69,70,71,238} Cigarette smoking,⁷² *H. pylori* infection,^{73,74} Epstein-Barr virus,⁷⁵ radiation

exposure, and prior gastric surgery for benign ulcer disease also have been implicated as risk factors.⁷⁶ Together, these data support the concept that gastric AC is often influenced by nutritional, socioeconomic, and medical factors rather than dominated by genetic predisposition. Awareness and decreased exposure to these factors have contributed to the decline in incidence and mortality rate of gastric AC in the United States.

Genetic risk factors include type A blood, pernicious anemia, a family history of gastric AC, hereditary nonpolyposis colon cancer (HNPCC), Li-Fraumeni syndrome, and hereditary diffuse gastric cancer (HDGC) caused by mutations in the E-cadherin gene, CDH1.^{77,78,79} HDGC is a genetic predisposition syndrome characterized by a family history of gastric AC characterized by poorly cohesive, diffuse-type histology, often with early onset of disease (generally younger than age 40 years); it accounts for <5% of gastric cancers. The cumulative risk of the development of diffuse gastric AC by the age of 80 years for CDH1 mutation carriers is 70% for men and 56% for women. Women are also at higher risk for the development of lobular breast cancer, with a cumulative risk of 42% by age 80 years. Individuals with a germline mutation in CDH1 should undergo a risk-reducing prophylactic gastrectomy to prevent future development of HDGC.⁸⁰ The optimal timing of prophylactic gastrectomy is unknown and is usually highly individualized. The current consensus is that the procedure should be discussed and offered to carriers of pathogenic germline CDH1 mutation in early adulthood, generally between ages 20 and 30 years.

Results from several studies have demonstrated an increased likelihood of *H. pylori* infection in patients with gastric AC, particularly cancer of the distal stomach.^{73,74} *H. pylori* infection is relatively common. About 30 to 40% of people in the United States get an *H. pylori* infection.⁶⁸ Most people get it as a child. It is thought that *H. pylori* spreads by unclean food and water, or through contact with an infected person's saliva and other body fluids; therefore it can track with families living together in close proximity. *H. pylori* usually does not cause symptoms. But it can break down the inner protective coating in some people's stomachs and cause inflammation. This can lead to gastritis or a peptic ulcer. Although cancer does not develop in most people with *H. pylori* infections, the known increased risk for patients to develop cancer who are infected has raised the issue of whether treatment of *H. pylori* might decrease the risk of gastric AC. Although the role of *H. pylori* in gastric carcinogenesis is well defined, no definitive evidence shows that mass eradication could reduce the incidence of gastric cancer.⁸¹ A large Chinese study showed no benefit in the prevention of gastric AC with the eradication of *H. pylori*.⁸² By contrast, a meta-analysis suggested that eradication, indeed, could reduce the risk of gastric AC.^{83,84} At present, treatment of patients with this infection is reserved for those with demonstrated ulcers, gastritis, or other symptoms.⁶⁰

Clinical presentation, diagnosis and staging of GECs

The most common clinical presentation of esophageal SCC and GEJ AC is dysphagia (problems swallowing). Cachexia and substantial weight loss are complications of this presenting symptom, which cause many patients to be debilitated at the time of the diagnosis. Another common presentation is occult or frank bleeding (usually manifested by melena, iron-deficiency anemia, and fatigue).⁶⁴ Other symptoms include treatment-refractory heartburn. It is not uncommon that patients have symptoms of chronic heartburn and dyspepsia, having

taken over the counter antacid and heartburn medications for years before finally being evaluated and ultimately being diagnosed with gastroesophageal cancer and its precursor lesions as the etiology of those symptoms. Patients with more proximal tumors can have tracheobronchial invasion and may present with laryngeal nerve paralysis, cough, and/or post-obstructive pneumonia.⁸⁵

Because of vague symptoms that go unaddressed for some time, it is unfortunately common for patients with GEA to present with synchronous metastatic disease when symptoms become more severe, persistent, and compounded by metastatic spread. Common sites of disseminated disease are liver, lung, distant lymph nodes, bone, and peritoneum. Carcinomatoses are common and seen in approximately 30% of patients with GA and 10% to 15% with GEJ AC (particularly diffuse and mixed-type histology, and tumors with signet-ring features), and result in the formation of ascites and abdominal pain culminating in severe anorexia, dysfunctional bowel, and, ultimately, frank partial or complete bowel obstructions.⁶⁴

Introduction to Pancreas Cancer:

Exocrine pancreatic cancer is a substantial health problem in the United States, with an annual incidence of 56,770 cases and death occurring in 45,750 patients annually.^{33,48} The nonhereditary risk factors for pancreatic cancers include older age, diabetes, chronic pancreatitis, intraductal pancreatic mucinous neoplasms, cigarette smoking, obesity, physical inactivity, and a diet high in saturated fats.⁸⁶ More recent data suggest pathogenic germline alterations may be present in up to 20% of unselected exocrine pancreatic cancers and has led to the recommendation for universal testing of patients with pancreatic cancer for germline mutations regardless of family history.^{87,88}

Symptoms associated with pancreatic cancer at the time of presentation commonly include abdominal pain with or without back pain, cachexia, and/or jaundice.^{89,90} Initial symptoms are often vague and can vary based on location, with pancreatic head lesions more likely to cause jaundice, and tail lesions, which often can be asymptomatic and, thus, delay diagnosis. When evaluating patients with adult-onset diabetes without other risk factors or worsening diabetes without an obvious cause, physicians should consider pancreatic cancer as a possible diagnosis.⁹¹ Although pancreatic cancer is staged using the standard TNM methodology, in practice, it is often classified as resectable, borderline resectable, locally advanced unresectable, or metastatic.

Introduction to Hepatobiliary Cancer:

Primary hepatobiliary cancers are a heterogenous group of cancers, which include hepatocellular carcinomas (HCCs), cholangiocarcinomas, and gallbladder cancers, and they represent the highest global incidence of solid-organ tumors and are responsible for approximately 1 million deaths annually, although they are less common in western cultures (particularly HCCs).^{33,48} The risk factors for HCC are well known and include cirrhosis of any etiology.^{92,93,94} Hepatitis B virus infections account for approximately 60% of all liver cancer incidence in developing countries and for approximately 23% of liver cancer in developed countries; the corresponding percentages for hepatitis C virus infections are 33% in developing

countries and 20% in developed countries. Hepatitis B infection can be decreased by vaccination. Hepatitis C now has effective therapy to eradicate the viral infection, which may lead to fewer cases of HCC in the coming years. In the United States and several other western countries with low-risk populations, alcohol-related cirrhosis and, nonalcoholic fatty liver disease also referred to as nonalcoholic steatohepatitis (NASH), associated with obesity, are thought to account for most liver cancers.^{93,94} The metabolic syndrome, which is defined to include diabetes (hyperglycemia, or high blood sugar), obesity, dyslipidemia (high serum triglycerides and/or high cholesterol), hypertension,⁹⁵ and microalbuminuria, is increasing in the United States,⁹⁶ and becoming a more common risk factor for all cancers,^{97,98,99} including liver cancer via NASH.^{100,101}

The total mortality from HCC in the United States has been increasing due to alcohol-related cirrhosis and, possibly, nonalcoholic fatty liver disease, despite the encouraging reduction in mortality associated with hepatitis C virus–related HCC.

Biliary tract cancers (cancer of the bile duct and gallbladder) include a diverse group of cancers, including intrahepatic cholangiocarcinoma (IHCC), hilar cholangiocarcinoma, extrahepatic cholangiocarcinoma (EHCC), and gallbladder cancer. Historically, these were considered a uniform entity, but they now are recognized to be quite distinct in terms of etiology, molecular biology, and, most recently, treatment.^{102,103,104,105} In western countries, cholangiocarcinoma is associated with metabolic syndrome/NASH,^{97,100} inflammatory bowel disease, primary sclerosing cholangitis, and hepatolithiasis, whereas the liver fluke and hepatitis B virus are important risk factors in Asian countries.¹⁰⁶ Cholangiocarcinoma is most common in women older than 50 years. A number of risk factors for gallbladder cancer have been described and include:

- obesity/metabolic syndrome,
- female sex,
- family history,
- middle age,
- gallstones causing chronic inflammation,
- porcelain gallbladder (ie, hardened gallbladder due to calcium deposits),
- ethnicity (highest in Mexican, Latin Americans, and Native Americans),
- choledochal cysts (ie, bile-filled sacs along the common bile duct),
- gallbladder polyps,
- abnormalities of the bile ducts causing backflow, and
- primary sclerosing cholangitis.¹⁰⁶

Recent molecular studies have demonstrated distinct molecular profiles between the anatomic sites and geographic or etiologic subsets.^{107,108,109,110} Cancers (adenocarcinomas) of the extrahepatic bile duct and gallbladder are relatively rare, with only 11,740 cases diagnosed annually in the United States, resulting in approximately 3,830 deaths annually.^{33,111}

Unfortunately, US statistics do not give specific numbers for IHCCs but classify them under “hepatobiliary tumors”; the actual incidence of biliary cancers as a whole is definitely higher, perhaps approaching the incidence of esophageal cancers, with approximately 15,000 cases

per year.¹¹² ACs of unknown primary site involving the liver are more commonly recognized as primary IHCCs, which has also led to an increase in incidence of the disease.¹¹³

There is a wide array of presentations of HCC, from asymptomatic disease found at screening to decompensated cirrhosis or paraneoplastic syndromes. Guidelines disseminated from several consensus conferences and professional organizations have recommended HCC surveillance in patients with cirrhosis who are at high risk for development of HCC.¹¹⁴ Ultrasound and serum α -fetoprotein (AFP) are the most commonly used modalities for HCC surveillance. Fibrolamellar cancer is generally seen in younger patients, is much more likely to be resectable, and is less commonly associated with infection or cirrhosis.¹¹⁵ In contrast, traditional HCC is found more often in men older than 65 years. Cholangiocarcinomas typically present with jaundice, pain, anorexia, abnormal laboratory test results, or with a mass evident on CT scan or ultrasound or that is visualized endoscopically.¹¹⁶ Gallbladder cancer often presents as vague postprandial right upper quadrant pain and is diagnosed as gallstones, with incidental finding of gallbladder cancer at the time of resection and/or in the pathology specimen.¹¹⁷ The location of the primary tumor often dictates which of these symptoms predominantly occur, such as painless jaundice with extrahepatic cholangiocarcinoma that is quite similar that seen with pancreatic cancer.

Introduction to Colorectal Cancer:

Colorectal cancers are cancers that arise in the large colon, which is comprised of the Cecum/appendix, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. The cancer precursor cells arise from the epithelial cells (the mucosal inner lining of the colon), and are carcinomas that have mucus gland differentiation, and are thus ‘adenocarcinomas’. Annually, approximately 147,950 new cases of large bowel cancer will be diagnosed, 104,610 of which are colon cancer, and the remainder rectal cancer.⁴⁷

Colon cancer etiology has been associated with a number of contributing factors,¹¹⁸ including genetic syndromes,^{7,8} high fat and red meat diet,^{119,120,121} obesity/metabolic syndrome,^{19,97,122} sedentary lifestyle,^{123,124} diabetes,¹²⁵ radiation,¹²⁶ inflammatory bowel disease,¹³³ asbestosis,^{127,128} and tobacco and alcohol.¹²⁹ It is common to have more than one of these associated risk factor, as they often track together, and it is likely that having many of these factors will heighten the risk of developing colorectal cancer.

Colon cancers start at level of an individual cell within the mucosa (the most superficial layer in the colon that serves as the inner layer of the ‘tube’) that acquires genetic alteration.¹³¹ The initial pathology is the formation, usually, of a polyp.¹³¹ A polyp is a mass of hyperplastic cells that forms a pedunculated polyp into the colon lumen. Over time accumulation of more genetic alterations in tumor suppressor and oncogenes within cells in the polyp lead to a ‘transformed’ and invasive component of the polyp which is malignant.^{5,132} Over more time, the cancer can travel through the lymphatic system and/or the blood to spread to distant sites in the body. There is therefore a long period of time on the order of decades, generally, from inception of the colonic preneoplastic cell(s) of origin and then progression toward invasive neoplasia (stage I), and then to higher stages (stages II-IV) of the cancer. This carcinogenesis model of colorectal cancer is well-established.⁵

Multiple screening tests are available to detect adenomatous polyps and colorectal cancer (CRC) before they become symptomatic. Tests for CRC differ with regard to sensitivity and specificity, frequency of testing, evidence of effectiveness, convenience, safety, availability, and cost. A general gold standard has been colonoscopies.³⁹ In addition to the USPSTF colon cancer screening recommendations for average risk individuals (the general population) to initiate at age ≥ 45 due to the association of colon cancer risk and age, as discussed above, there are recommendations to screen at younger ages for higher risk individuals including those with family or personal history of colorectal cancer and/or a known genetic predisposition syndrome such as Lynch syndrome,^{7,8} or inflammatory bowel disease.¹³³

There are no medical societies that list NDMA as a risk factor for gastrointestinal cancers as a consideration of etiology (whether gastric AC, hepatobiliary, pancreatic or another type), nor do any guidelines suggest that treatment of screening/surveillance of gastrointestinal cancer is changed in any way for patients who might have been exposed to NDMA impurities in VCDs.

8b. Introduction to other Upper Aerodigestive Cancers

Upper aerodigestive cancers include lung and oropharyngeal cancers. In 2018, the incidence of new cases of lung and respiratory tract cancers was 218,520 cases (age adjusted rate 54/100,000 people) and 142,080 people died of this cancer (age adjusted rate 35/100,000 people). In 2018, the incidence of new cases of oropharyngeal cancers was 46,667 cases (age adjusted rate 12/100,000 people) and 10,185 people died of this cancer (age adjusted rate 3/100,000 people). Another closely related cancer, laryngeal cancer, had 12,023 new cases, and 3,777 people died of this cancer. For every 100,000 people, 3 new Laryngeal cancer cases were reported and 1 people died of this cancer.³⁴

Introduction to Lung Cancer

Overall, lung cancer causes more deaths than breast, prostate, colorectal, and brain cancers combined.^{33,111} Lung cancer deaths are declining in men and women, largely due to decreases in smoking. Now, however, nearly one-half of all lung cancer deaths occur in women. The term lung cancer, or bronchogenic carcinoma, refers to malignancies that originate in the airways or lung cells (parenchyma). Approximately 95 percent of all lung cancers are classified as either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC) with the majority being NSCLC (~80-85%) vs SCLC (~15%). This distinction is required for proper staging, treatment, and prognosis. Other cell types comprise about 5 percent of malignancies arising in the lung. The main subtypes of NSCLC are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. These subtypes, which start from different types of lung cells are grouped together as NSCLC because their treatment and prognoses (outlook) are often similar.

Similar to many cancers, advances in understanding the molecular pathogenesis of NSCLC have demonstrated that NSCLC is a heterogeneous group of diseases. Although the initial treatment of localized disease is the same generally at this time, the molecular characterization

of tumor tissue in patients with NSCLC serves as a guide to treatment both in those who present with metastatic disease and in those who relapse after primary therapy.

Smoking is by far the leading risk factor for lung cancer. About 80% of lung cancer deaths are thought to result from smoking and this number is probably even higher for small cell lung cancer (SCLC). It's very rare for someone who has never smoked to have SCLC. The risk of lung cancer for people who smoke is many times higher than for people who don't smoke. The longer you smoke and the more packs a day you smoke, the greater your risk. Cigar smoking and pipe smoking are almost as likely to cause lung cancer as cigarette smoking. Smoking low-tar or "light" cigarettes increases lung cancer risk as much as regular cigarettes. Smoking menthol cigarettes might increase the risk even more since the menthol may allow people to inhale more deeply. If you don't smoke, breathing in the smoke of others (called secondhand smoke or environmental tobacco smoke) can increase your risk of developing lung cancer. Secondhand smoke is thought to cause more than 7,000 deaths from lung cancer each year.¹³⁴

Radon is a naturally occurring radioactive gas that results from the breakdown of uranium in soil and rocks. It cannot be seen, smelled, or tasted. Radon is the second leading cause of lung cancer in this country, and is the leading cause among people who don't smoke. Outdoors, there is so little radon that it is not likely to be dangerous. But indoors, radon can be more concentrated. Breathing it in exposes your lungs to small amounts of radiation. This may increase a person's risk of lung cancer. Homes and other buildings in nearly any part of the United States can have high indoor radon levels (especially in basements).¹³⁵

People who work with asbestos (such as in mines, mills, textile plants, places where insulation is used, and shipyards) have a higher risk of being diagnosed with and dying from lung cancer. Lung cancer risk is much greater in workers exposed to asbestos who also smoke. It is not clear how much low-level or short-term exposure to asbestos might raise lung cancer risk. People exposed to large amounts of asbestos also have a greater risk of developing mesothelioma, a type of cancer that starts in the pleura (the lining surrounding the lungs).

Other carcinogens found in some workplaces that can increase lung cancer risk include radioactive ores such as uranium, inhaled chemicals such as arsenic, beryllium, cadmium, silica, vinyl chloride, nickel compounds, chromium compounds, coal products, mustard gas, and chloromethyl ethers, and diesel exhaust.¹³⁶ Also, air pollution in cities especially near heavily trafficked roads may raise the risk of lung cancer.¹³⁷ Marijuana is possibly also associated with increased risk.^{138, 139, 140}

Lung cancer history in the family may also lead to a higher personal risk of lung cancer – however how much is genetic versus exposure to the same environmental and household exposures is not clear.¹⁴¹

Overall, despite these many possible risks above for lung cancer, the vast majority of cases are solely due to tobacco smoking.¹¹¹ It is also notable that many other cancers are associated with tobacco smoking as discussed in other sections of this report. People with an extensive history of (or current) smoking have been shown to have improved clinical detection and lung-cancer mortality¹⁴² via routine CT screening of the chest.^{134, 143}

It is notable that smoking increased hypertension in addition to its carcinogenic effects, and thus increases hypertensive related disease including cardiac, renal, and other hypertensive-related medical problems.^{144,145,146} Therefore there is a significant and well-established relationship between tobacco use and use of antihypertensive medications, including VCDs.

Introduction to Pharyngeal Cancer

Head and neck cancers can have many different names depending on where the cancer starts. For example, cancers that start in the throat (pharynx), can be called nasopharyngeal (for the upper throat behind the nose), oropharyngeal (for the middle throat behind the mouth), or hypopharyngeal (for the lower throat). Oropharyngeal squamous cell carcinomas (SCCs) originate in the soft palate, tonsils, base of tongue, pharyngeal wall, or vallecula (the fold located between the base of tongue and the epiglottis). Historically, tobacco and alcohol were the principal risk factors associated with oropharyngeal cancer. However, there has been a shift in the epidemiology of this disease, with a significant increase in cases due to human papillomavirus (HPV) infection and a decrease in cases associated with tobacco and alcohol.^{147, 148} Infection with certain types of HPV can cause some forms of cancer, including cancers of the penis, cervix, vulva, vagina, anus, mouth, and throat. In certain other areas of the world, many people chew betel quid, which is made up of areca nut (betel nut), spices, lime, and other ingredients. Many people in these areas also chew gutka, a mixture of betel quid and tobacco. People who chew betel quid or gutka have a recognized increased risk of cancer of the mouth. Other associated factors include obesity, higher age, diet low in fruits and vegetables.

There are no medical societies that list NDMA as a risk factor for upper aerodigestive cancers as a consideration of etiology, nor do any guidelines suggest that treatment of screening/sureveillance of upper aerodigestive cancer is changed in any way for patients who might have been exposed to NDMA impurities in VCDs.

8c. Introduction to Genitourinary Cancer

“Genitourinary cancers” encompass a variety of heterogeneous cancers that arise from the urinary tract or urogenital system (urinary bladder, ureters, prostate, penis, uterus, cervix, and vagina). In 2018, the incidence of new cases of genitourinary cancers of interest (urinary bladder, kidney, prostate and uterus) combined was 413,155 cases (age adjusted rate 170/100000 people) and 73,501 people died of these cancers (age adjusted rate 32/100000 people).³⁴

Introduction to Bladder Cancer

Bladder cancers are the most common genitourinary malignancy in both men and women. In 2018, the incidence of new cases of urinary bladder cancers was 77,443 cases (age adjusted rate 17/100000 people) and 14,134 people died of this cancer (age adjusted rate 4/100000 people).³⁴ Bladder cancers are broadly categorized as urothelial and non-urothelial, where approximately 90% of bladder cancers are urothelial.¹⁴⁹ Non-urothelial bladder cancer

accounts for less than 5 percent of all bladder tumors, and approximately 90 percent of non-urothelial bladder cancers are epithelial in origin, and these include squamous cell carcinoma, adenocarcinoma, and small cell carcinoma. Non-epithelial tumors include sarcoma, carcinosarcoma, paraganglioma, melanoma, and lymphoma.

Unmodifiable risk factors of bladder cancer include age, sex, and ethnicity. Bladder cancer is typically diagnosed in older individuals. A majority (approximately 73 percent) of patients with bladder cancer are older than 65 years of age.¹⁵⁰ The age of onset is younger in current smokers than in never smokers.¹⁵¹ Although the overall incidence of bladder cancer is lower in females and African Americans, these groups have more advanced-stage tumors at presentation compared with Caucasian males.¹⁵² While there appears to be a small increased risk in relatives of those with bladder cancer, particularly in cancers diagnosed before age 60, the risk is influenced by smoking.¹⁵³ Lynch syndrome, classically a genetic predisposition to colorectal cancer, uterine cancer, and gastric cancer, also includes bladder cancer, which 5% of Lynch syndrome patients experience.¹⁵⁴

Modifiable risk factors of bladder cancer include cigarette smoke being the most important contributing factor to the overall incidence of urothelial cancer in western countries.¹⁵⁵ This database included over 465,000 individuals followed from 1995 to 2006 in the United States. For current smokers, there was a significant increase in the risk of bladder cancer for both males and females (multivariate adjusted hazard ratios [HRs] 3.89 and 4.65, respectively). Although there was an attenuation of risk in former smokers, the risk remained significantly elevated (HRs 2.14 and 2.52 for males and females, respectively). There was a small but statistically significant increase in the incidence of bladder cancer among males who smoked a pipe or cigars but not cigarettes (HR 1.29). Smoking cessation also appears to decrease the recurrence rate for patients with non-muscle-invasive bladder cancer even after the diagnosis.¹⁵⁶

In addition to cigarette smoke, occupations that have been linked to an increased risk of bladder cancer include metal workers, painters, rubber industry workers, leather workers, textile and electrical workers, miners, cement workers, transport operators, excavating-machine operators, and jobs that involve manufacture of carpets, paints, plastics, and industrial chemicals. Compounds potentially linked to bladder cancer include benzene, polyaromatic hydrocarbons, paint components, hair dye components and diesel exhausts, among others.¹⁵⁷

Other risk factors include chronic and recurrent bladder infections, HPV infection, previous radiation to the bladder, previous exposure to cyclophosphamide chemotherapy/immunosuppressant, and previous bladder surgery (augmentation cystoplasty). Overall, despite these many possible risks above for bladder cancer, the vast majority of cases are solely due to tobacco smoking.

It is notable that a positive association was observed between hypertension and urinary bladder cancer. In this study of 39,618 patients, during a total follow-up duration of 380,525 and 372,020 person-years in the hypertension and comparison non-hypertension groups, 248 and 186 patients developed UB cancer, respectively, representing a 32% increase in the risk (aHR, 1.32; 95% CI, 1.09-1.60). A separate population-based study using a similar dataset found no

impact from antihypertensive use on the risk of bladder cancer, after controlling for age, sex, urbanization level, occupation, income, diabetes, dyslipidemia, stroke, coronary heart disease, chronic obstructive pulmonary disease, alcoholism, and alcoholic liver damage derived a neutral risk (adjusted HR = 1.19; 95% CI, 0.80–1.77) in patients receiving antihypertensive agents versus those who were not.¹⁵⁸ This suggests that hypertension and its associated factors/comorbidities are linked with bladder cancer development.

Introduction to Kidney (Renal) Cancer

In 2018, the incidence of new cases of kidney cancers was 65,759 cases (age adjusted rate 18/100000 people) and 16,641 people died of this cancer (age adjusted rate 4/100000 people).³⁴ Renal cell carcinomas (RCCs), which originate within the renal cortex, are responsible for 80 to 85 percent of all primary renal neoplasms. Transitional cell carcinomas of the renal pelvis are the next most common (approximately 8 percent). Other parenchymal epithelial tumors, such as oncocytomas, collecting duct tumors, and renal sarcomas, occur infrequently. The most common histologic pattern of RCC is clear cell (75 to 85 percent). Papillary and chromophobe tumors constitute 10 to 15 and 5 to 10 percent, respectively. The VHL gene is found on chromosome 3 (3p25 to 26) and plays a pivotal role in the development of clear cell RCC in patients with VHL disease and sporadic RCC.^{159,160}

Unmodifiable risk factors of RCC include gender, where males are diagnosed twice as commonly as females.¹⁶⁰ Age is another risk factor, where RCC occurs predominantly in the sixth to eighth decade of life with median age at diagnosis around 64 years of age.¹⁶¹ The risk of a second, metachronous RCC is increased in patients who have been treated for one renal cancer. This increased risk is most pronounced with younger age at the first RCC, suggesting that early onset renal cancer has a genetic component.¹⁶² There are documented familial predispositions with RCC.¹⁶³ Patients with inherited polycystic disease may have an increased risk of RCC (as well as liver and colon cancer), even in the absence of kidney dysfunction or end-stage kidney failure.¹⁶⁴

Modifiable risk factors of RCC include smoking,¹⁶⁵ hypertension,¹⁶⁶ obesity,¹⁶⁷ hemodialysis patients with acquired polycystic kidney disease,¹⁶⁸ and occupational exposure, including cadmium, asbestos, and petroleum byproducts.¹⁶⁹ Prior radiation and chemotherapy have also been associated with RCC.^{170,171}

It is notable that a positive association was observed between hypertension and urinary renal cancer.^{22,23} Using nationally representative data from the Korean National Health Insurance System, 9,746,445 participants without kidney cancer between January 1, 2006 and December 31, 2009 were followed up until December 31, 2017 to obtain data regarding cancer incidence. Participants were categorized, according to blood pressure, as normal (<120/80 mm Hg), elevated (120-129/<80 mm Hg), and hypertensive (\geq 130/80 mm Hg) with or without antihypertensive medication. Participants with hypertension were at higher risk for kidney cancer than those without hypertension.¹⁷² Another study demonstrated that hypertension is associated with renal cell cancer, and the hypertension resolved after undergoing nephrectomy (removal of the RCC), suggesting that RCCs may cause hypertension.¹⁷³

Introduction to Prostate Cancer

Prostate cancer is the second most common cancer in men worldwide, only second to lung cancer. In 2018, the incidence of new cases of prostate cancers was 211,893 cases (age adjusted rate 107.5/100,000 people) and 37,488 people died of this cancer (age adjusted rate 19/100,000 people).³⁴ The current lifetime risk of prostate cancer for men living in the United States is estimated to be approximately one in eight men. The incidence is highly dependent on screening with prostate-specific antigen (PSA), and the number of PSA-driven biopsies, because many of these cancers remain indolent, latent, and occult, and more often than not patients die with the cancer, not from it. Therefore, more intense screening for it will identify more, but not necessarily change overall survival rates from prostate cancer. Indeed, as above, the USPSTF recommends PSA testing for prostate cancer screening with low grade, only for “selected patients depending on individual circumstances” (Grade C) for men between the ages of 55-69, while they recommend against screening (Grade D) for men ages >70.^{43,44} Prostate cancer has a strong inherited component and men with a family history of prostate cancer on either side of the family, particularly those with a first-degree relative who was diagnosed at age <65 years, are at increased risk for prostate cancer,^{174,175} and this is where increased screening is generally recommended. A central argument against routine PSA screening otherwise is that many of these cancers, if left undetected, would never have become clinically meaningful during a man's lifetime.

Unmodifiable risk factors include obviously gender, but also most importantly age. Prostate cancer has the strongest relationship between age and any human cancer. The widespread prevalence of occult prostate cancer in older men and the dramatic increase with age are illustrated by a review of autopsy studies conducted in multiple countries.¹⁷⁶ This autopsy series showed that the incidence of occult prostate cancer increased with age in men (age 20 to 30 years, 2-8%; 31-40 years, 9-31%; 41-50 years, 3-43%; 51-60 years, 5-46%; 61-70 years, 14-70%; 71-80 years, 31-83%; 81-90 years, 40-73%). The variability between reports may reflect differences in pathologic techniques, or geographic differences due to environmental or ethnic factors. Another unmodifiable risk factor is ethnic factors, where prostate cancer is more common in African American men, compared to Caucasian and Hispanic men. The annualized average incidence rates for men in the early 70s per 100,000 people, is approximately 1600, 1000, and 700 for African American men, compared to Caucasian and Hispanic men, respectively.¹⁷⁷ As above, another risk factor for prostate cancer is inherited predisposition, particularly in family members diagnosed at younger age.

Modifiable risk factors include cigarette smoke, particularly in African Americans.¹⁷⁸ Moreover, data suggest an association of smoking at the time of diagnosis with risk of a prostate cancer recurrence and cancer-related mortality.^{179,180} Other risk factors include obesity,^{181,182,183} sedentary lifestyle,¹⁸⁴ infection,¹⁸⁵ and environmental carcinogens including agent orange, chlordecone (insecticide), and bisphenol A estrogen. Hypertension has been found to have a small increased risk of prostate cancer in a meta-analysis (RR 1.08, 95% CI 1.02-1.15, p=0.014).¹⁸⁶ There was a significant heterogeneity among the included studies, and therefore residual confounding are possible. There has been an association of prostate cancer and infertility.¹⁸⁷ An association between ejaculatory frequency and a lower risk of prostate cancer has been suggested.^{188,189} Exposure to ultraviolet light, likely increasing vitamin D, and

vitamin D have been associated with a protective effect on the development of prostate cancer.^{190,191}

Of all the factors discussed and associated with prostate cancer, increasing age is by far the most important factor.

Introduction to Uterine Cancer

In 2018, the incidence of new cases of uterine cancers (or endometrial cancer) was 58,060 cases (age adjusted rate 27.5/100000 people) and 11,238 people died of this cancer (age adjusted rate 5/100000 people).³⁴ The incidence peaks between ages 60 and 70 years, but 2 to 5 percent of cases occur before age 40 years. Uterine cancers are broadly classified into two major types that have different clinicopathologic characteristics and risk factors (Type 1, and Type 2).¹⁹² Type 1 neoplasms have low-grade (International Federation of Gynecology and Obstetrics [FIGO] grades 1 and 2) endometrioid histology and comprise the majority (80 percent) of uterine cancers. The less common type 2 neoplasms (FIGO grade 3 endometrioid histology and nonendometrioid histologies: serous, clear cell, mixed cell, undifferentiated, carcinosarcoma) are typically not estrogen-sensitive. Risk factors include lower body mass index, non-White race, and older age.

The primary risk factor for type 1 uterine cancer is long-term exposure to increased estrogen levels from an exogenous or endogenous source without adequate opposition by a progestin. Lynch syndrome is a genetic risk factor for several cancers, including uterine cancer. There is an increasing incidence of uterine cancer, associated with increasing prevalence of obesity, decreasing use of menopausal hormone therapy with progestins, increasing prevalence of diabetes, and changes in reproductive behaviors (e.g., increasing prevalence of nulliparity or no children).¹⁹³ Patients deemed to be at high risk (eg. Lynch syndrome) for developing uterine cancer have strategies to prevent it, including hysterectomy and/or mitigating as well as their underlying risk factors. Hysterectomy is the most aggressive approach; more conservative approaches include achieving and maintaining a normal body mass index and using progestin-dominant contraceptives. Estrogen-progestin or progestin-only contraceptives are protective factors.

There are no medical societies that list NDMA as a risk factor for genitourinary cancers (including bladder, renal, prostate, and uterine cancers) as a consideration of etiology, nor do any guidelines suggest that treatment of screening/surveillance of genitourinary cancer is changed in any way for patients who might have been exposed to NDMA impurities in VCDs.

8d. Introduction to Breast Cancer

Globally, breast cancer is the second most frequently diagnosed malignancy just behind lung cancer. In 2018, the incidence of new cases of breast cancers was 254,744 cases (age adjusted rate 127/100000 people) and 16,641 people died of this cancer (age adjusted rate 4/100000 people).³⁴ The incidence rates are highest in North America, Australia/New Zealand, and in western and northern Europe and lowest in Asia and sub-Saharan Africa. These international differences are likely related to societal changes as a result of industrialization (eg, changes in

fat intake, body weight, age at menarche, and/or lactation, and reproductive patterns such as fewer pregnancies and later age at first birth).

Modifiable risk factors associated with increased incidence of breast cancer in women include alcohol, obesity, sedentary lifestyle, no children, not breastfeeding, birth control, hormonal therapy after menopause, and breast implants (with a rare type of breast cancer). Factors that cannot be modified include female gender, older age, germline (inherited) genetic risk and family history of breast cancer, personal history of breast cancer, ethnicity (higher in African American women), dense breast tissue, benign breast conditions like lipomas and many others, early onset menstruation, late menopause (after age 55), and prior radiation to the chest. There are no medical societies that list NDMA as a risk factor for breast cancer as a consideration of etiology, nor do any guidelines suggest that treatment of screening/surveillance of breast cancer is changed in any way for patients who might have been exposed to NDMA impurities in VCDs.

As noted above, due to the high incidence of commonality of breast cancer in the United States, routine screening is recommended by the USPSTF starting at age 50 in all women. However, up to 15 percent of women are diagnosed with breast cancer due to the presence of a breast mass that is not detected on mammogram (mammographically occult disease), and another 30 percent present with a breast mass in the interval between mammograms (interval cancers).¹⁹⁴ As noted, patients with known inherited pathogenic gene mutations in BRCA1, BRCA2, or others are recommended to start screening earlier, and also consider prophylactic mastectomies to decrease risk of breast cancer mortality.

There are no medical societies that list NDMA as a risk factor for breast cancers a consideration of etiology, nor do any guidelines suggest that treatment of screening/surveillance of breast cancer is changed in any way for patients who might have been exposed to NDMA impurities in VCDs.

8e. Introduction to Hematologic (Blood) Cancer

“Hematologic cancer” is a broad term that includes a number of heterogeneous malignancies including leukemias, myelomas, and lymphomas. The malignant cells interfere with production of normal blood cells, causing weakness, infection, bleeding, and other symptoms and complications. In 2018, the incidence of new cases of leukemia was 50,174 cases (age adjusted rate 13/100,000 people) and 23,503 people died of this cancer (age adjusted rate 6/100,000 people). In 2018, the incidence of new cases of myeloma was 26,593 cases (age adjusted rate 7/100,000 people) and 12,326 people died of this cancer (age adjusted rate 3/100,000 people). In 2018, the incidence of new cases of non-Hodgkin lymphoma was 71,005 cases (age adjusted rate 18/100,000 people) and 20,287 people died of this cancer (age adjusted rate 5/100,000 people). In 2018, the incidence of new cases of Hodgkin lymphoma was 8,385 cases (age adjusted rate 3/100,000 people) and 1,038 people died of this cancer (age adjusted rate <1/100,000 people).³⁴

Each of the many hematologic neoplasms are relatively rare. Acute myelogenous leukemia (AML) is the most common form of acute leukemia, rapidly growing cancers that originate in

the bone marrow. AML has a median age of diagnosis of approximately 65 years, and the incidence increases with age.¹⁹⁵ AML has been associated with environmental factors (eg, exposure to chemicals, radiation, tobacco, chemotherapy, retroviruses). In rare cases, AML in adults is associated with inherited genetic abnormalities.

Chronic myeloid leukemia (CML; also known as chronic myelocytic, chronic myelogenous, or chronic granulocytic leukemia) is a myeloproliferative neoplasm characterized by the dysregulated production and uncontrolled proliferation of mature and maturing granulocytes with fairly normal differentiation. CML accounts for approximately 15 to 20 percent of leukemias in adults. Exposure to ionizing radiation is the only known risk factor.^{196,197} Rare families in which multiple members develop myeloproliferative neoplasms (MPNs), including CML, have been described.¹⁹⁸

Lymphomas, cancers of the lymphatic system, are very heterogeneous subgroup of cancers, divided broadly into non-Hodgkin (NHL) and Hodgkin (HL) lymphomas. Diffuse large B cell lymphoma (DLBCL) is the most common histologic subtype of NHL accounting for ~25% of NHLs. Incidence increases with age; the median age at presentation is 64 years for patients as a whole. DLBCL is a heterogeneous group of tumors. Familial aggregation of patients with DLBCL and other NHL subtypes has been noted.¹⁹⁹

Multiple myeloma (MM) is a relatively uncommon cancer accounting for approximately 1 to 2 percent of all cancers and slightly more than 17 percent of hematologic malignancies and is typically characterized by the neoplastic proliferation of plasma cells producing a monoclonal immunoglobulin. The plasma cells proliferate in the bone marrow and can result in extensive skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic fractures. MM is largely a disease of older adults. The median age at diagnosis is 65 to 74 years.²⁰⁰ The incidence varies by ethnicity; the incidence in African Americans and Black populations is two to three times that in Whites populations in studies from the United States.²⁰¹ The risk of MM increases with body mass index.²⁰² A small fraction of cases are familial.²⁰³

In summary, hematologic cancers are a very heterogeneous group of disorders, each of which are relatively rare. There are no medical societies that list NDMA as a risk factor for hematologic cancers or for consideration of etiology, nor do any guidelines suggest that treatment of screening/sureveillance of hematologic cancer is changed in any way for patients who might have been exposed to NDMA impurities in VCDs.

8f. Introduction to Cancers Summary

Cancer is common in the United States, accounting for approximately 25% of all deaths annually (1 in 4 people). However, cancer is not a uniform disease, but rather a large group of heterogeneous cancers, even within a cancer type from the same anatomical site. They are heterogeneous in terms of etiology and risk factors, biology, prognosis, treatments, and survival. Common and unifying risk factors across many cancers include those that are not modifiable such as higher age, as well as gender (e.g. prostate in men, breast cancer in women), as well as modifiable risk factors like obesity, smoking, high fat and low fibre diets, and

sedentary lifestyle. Notably, each of those modifiable risk factors for all these types of cancer are also comorbidities commonly observed in hypertensive patients.

In all the cancers reviewed above, there are no medical societies that list NDMA as a risk factor to consider as to the etiology of the cancers nor to counsel to avoid exposure to, nor do any guidelines suggest that treatment or screening/surveillance of any of the cancers should be changed in any way for patients who might have been exposed to NDMA impurities in VCDs.

9. Valsartan and valsartan containing drugs (VCDs)

9a. Background: Generic medications incorporating valsartan

According to the CDC, nearly half of adults in the United States (108 million, or 45%) have hypertension defined as a systolic blood pressure ≥ 130 mm Hg or a diastolic blood pressure ≥ 80 mm Hg, or are taking medication for hypertension. Valsartan is an angiotensin II receptor antagonist (ARB) and works as a anti-hypertensive agent by blocking the effects of angiotensin.^{204,205} The maximum dose of valsartan is 320 mg per day. It also became available in combination with other anti-hypertensive drugs, such HCT (valsartan and hydrochlorothiazide) or amlodipine.

ARBs in addition to standard anti-hypertensive medical therapy, are generally intended for use in patients with acute myocardial infarction (MI, 'heart attack') who are at high risk of a subsequent cardiovascular event (i.e. those with heart failure, left ventricular ejection fraction ≤ 40 percent, diabetes, or chronic kidney disease).²⁰⁶ The addition of an ARB to standard medical therapy (including antiplatelet therapy, beta blocker, and statin) in patients with recent myocardial infarction (MI) improves cardiovascular outcomes.²⁰⁶ In this scenario, the therapy is recommended indefinitely.

In summary, hypertension is a common illness in the United States and a significant risk factor for the development of cardiovascular disease, the leading cause of mortality. Antihypertensive drugs, including VCDs, are routinely and commonly prescribed to treat hypertension and complications of cardiovascular disease.

9b. VCDs and other ARBs Are Not Associated With an Increased Cancer Risk

On July 2010, FDA communicated its intent to conduct a safety review of ARBs after a published meta-analysis of 5 randomized clinical trials reported a small but statistically significant increase in risk of cancer in patients taking an ARB compared to patients not taking an ARB.²⁰⁷ To further evaluate the reported link between use of ARBs and cancer, FDA conducted a trial-level meta-analysis of clinical trials in which patients had been randomized to an ARB treatment or a non-ARB treatment, including 31 trials and approximately 156,000 patients, far more than the approximately 62,000 in the previously published analysis.

FDA's more comprehensive meta-analysis did not show an increased risk of cancer in the patients taking an ARB medication as reported on June 2, 2011.²⁰⁸ The FDA reported "The 31 trials included 84,461 patients randomized to ARBs and 71,355 patients randomized to non-

ARB comparators, with an average follow-up of 39 months. The rate of incident cancer events in the ARB group was 1.82 per 100 patient-years, and the rate in non-ARB comparators was 1.84 per 100 patient-years. The relative risk of incident cancer in patients taking ARBs was 0.99 (95% confidence interval 0.92 to 1.06). The estimate of risk was similar irrespective of the choice of statistical method (random effects or fixed effects), as well as the choice of comparator arm used in the analysis (all comparators, placebo only, active-comparators only).” They also reported that they, “also found no evidence of association between ARBs and cancer-related death (relative risk 1.04, 95% confidence interval 0.96 to 1.13), breast cancer (odds ratio 1.06, 95% confidence interval 0.90 to 1.23), lung cancer (odds ratio 1.07, 95% confidence interval 0.89 to 1.29), or prostate cancer (odds ratio 1.05, 95% confidence interval 0.95 to 1.17).” These findings are consistent with other studies that all suggest no increased risk of cancer related to ARB use.^{209,210,211} In short, taking an angiotensin II receptor blocker, such as valsartan, is not associated with an increased risk of cancer.

In contrast, as discussed earlier in the report in the “Introduction to Cancer” and its subsections above, hypertension (the underlying condition for which valsartan and other ARBs are commonly prescribed) is associated with a number of known cancer-related risk factors, and also serves as an independent risk factor for cancer. Such an association of hypertension and cancer would be an example of protopathic bias/reverse causation,²¹² where “a pharmaceutical agent is inadvertently prescribed for an early manifestation of a disease that has not yet been diagnostically detected”,²¹² or in this case, anti-hypertensive medications prescribed for a condition (hypertension, congestive heart failure etc) that is closely associated with cancer-related risk factors (diabetes, obesity, metabolic syndrome) and also a risk factor in and of itself.^{23,24,209,213} As such, while taking valsartan does not increase one’s risk of any cancer, hypertension and its associated conditions (obesity, smoking, alcohol use, sedentary lifestyle, high fat diet, etc.) do increase an individual’s risk for numerous cancers, including the cancers at issue in this litigation. As such, we can expect that cancer incidence in the population of valsartan users will be higher than the incidence of those cancers among the general population. Simply put, correlation does not prove causation.

10. Relevant Background: VCDs with NDMA or other impurities

In June 2018, Zhenjiang Huahai Pharmaceuticals (ZHP), the manufacturer of the active pharmaceutical ingredient (API) for generic valsartan used by some of the Defendant pharmaceutical companies reported that it had detected the presence of a previously undetected impurity — NDMA — in the active pharmaceutical ingredient for valsartan. According to tests of a random selection of API batches performed by ZHP, the levels of NDMA ranged from 3.4 ppm to 120 ppm, with an average of 66.5 ppm.²¹⁴

On July 13, 2018, FDA announced a voluntary recall of several medicines containing valsartan. FDA’s announcement stated:

“The presence of NDMA was unexpected and is thought to be related to changes in the way the active substance was manufactured.” The FDA further noted that, **“because valsartan is used in medicines to treat serious medical conditions, patients taking the recalled valsartan-containing medicines**

should continue taking their medicine until they have a replacement product.” (emphasis added)

This suggests that the FDA’s assessment concluded that the risk of not taking the medication outweighed any potential risks of continuing taking the medication despite the trace impurity.²¹⁵ As FDA clarified on July 27, 2018, just two weeks later:

“NDMA has been found to increase the occurrence of cancer in animal studies. **These animal studies were done using amounts of NDMA much higher than the impurity levels in recalled valsartan batches.** Based on these animal studies, the U.S. Environmental Protection Agency considers NDMA a probable human carcinogen—a chemical that can increase the risk of cancer in humans. NDMA is found in some water supplies and in some foods. Consuming up to 96 nanograms NDMA/day is considered reasonably safe for human ingestion. It is estimated that **over the course of a person’s lifetime, consuming this amount [96ng/day or 0.096µg/day] of NDMA would result in less than one additional case of cancer for every 100,000 people. To put this in context, currently one out of every three people in the US will experience cancer in their lifetime.**” (emphasis added)²¹⁶

As discussed earlier the current estimate is that cancer accounts for 25% of all deaths in the United states (or 1 in 4 deaths) in 2018. However, the estimate over coming years takes into account the growing rate, and the FDA indicates here that in the future this will be ~33% of all deaths (or 1 in 3 deaths) that are due to cancer. In its announcement on July 27, 2018, FDA went on to say that,

“the amounts of NDMA found in the recalled batches of valsartan exceeded these acceptable levels. **The agency wanted to put some context around the actual potential risk posed to patients** who used versions of valsartan that may have contained high levels of NDMA. Based on records from the manufacturer of the recalled valsartan, **some levels of the impurity may have been in the valsartan-containing products for as long as four years.** FDA scientists estimate that **if 8,000 people took the highest valsartan dose (320 mg) from the recalled batches daily for the full four years, there may be one additional case of cancer over the lifetimes of these 8,000 people.** This assessment led to FDA’s decision to have these batches recalled”

It should be noted again, that there were 436 new cases of cancer in 2018 per 100,000 (or 4.36 cancers/1,000 people per year) in the United States - that is, 436 new cases per 100,000 people (or 4.36/1,000) *per year*. While this includes all cancers, the alledged cancer types in this litigation include all the most common cancers and others. Moreover, ‘over a lifetime’ which could be estimated to range for 30-50 years on average for patients taking these medications since most people with hypertension are already above the age of 40, there would be a total of 13,080-21,800 cancers diagnosed per 100,000 people (131-218 cancers per 1,000 people) over these 30-50 years at current incidence rates.

In contrast, the FDA's notification with regard to valsartan drugs estimated an additional 1/8,000 (or 0.125/1000, or 12.5 cancers diagnosed per 100,000 people) lifetime risk, or "70 years" versus 305 total cancers per 1000 people over 70 years at current incidence rates. This is a relatively low increased risk (0.125/1000 on top of 305/1000, which is 0.041% increased relative incidence due to NDMA over baseline incidence), and is derived from the assumption that all patients would take the highest doses of valsartan drugs throughout the full period in which the NDMA impurity had existed and that the impurity had existed at the highest level in each prescription used.

This 'worst case scenario' calculation has many assumptions that most if not all individuals would not meet. Obviously, many valsartan patients were not taking the highest (320mg) dose. Also, some doses tested did not have any level of detectable impurity and patients may have taken valsartan during this period that did not contain any trace amounts of NDMA/NDEA or that contained amounts below the current acceptable limits. As such, it is not reasonable to assume that FDA's 'worst case scenario' estimate of potential NDMA/NDEA exposure would actually apply to any plaintiff in this litigation. FDA stated the same, in January 2019:

"The vast majority of patients exposed to NDMA through ARBs received much smaller amounts of the impurity than this worst-case scenario. Since not all ARBs are affected, it's very likely that a patient taking an ARB for four years would not have always received one of the affected products." (emphasis added)²¹⁷

As set forth below, there is no reliable data which supports any actual increased risk of cancer from valsartan containing the NDMA impurity. Simply, there is significant reason to doubt that ingestion of NDMA at the trace levels detected in valsartan drugs, over the four years in which the impurity existed, would lead to any excess cancer risk. An individual's risk of developing any individual cancer type would be influenced much more significantly by their baseline factors and etiologies.

Further, because even the FDA's "worst case scenario" calculation is of such a low risk as compared against the life-saving value of valsartan to patients, the FDA reminded patients to continue to take valsartan until a replacement could be found. As FDA advised patients on August 30, 2018,

"Although the risk to patients taking the affected products is extremely low, we take matters of pharmaceutical quality very seriously. We took immediate steps to address these findings."

"However, we did not want patients taking valsartan to hear this news and abruptly stop their medications, possibly suffering serious medical issues, such as stroke."²¹⁸

FDA's advisory makes clear that the risk of cancer from valsartan containing the NDMA impurity is outweighed by the risks associated with discontinuing valsartan, again reflecting its value as a life-saving and life-prolonging medication. In short, if patients discontinued their ARB treatment, many more would die or suffer serious adverse consequences from cardiac

events than would be at risk for cancer, even under the FDA's own worst-case-scenario estimates.

The risk reduction in cardiovascular effects of antihypertensives in general, including VCDs and ARBs, was recently reported in a large meta-analysis, which demonstrated that improved blood pressure led to fewer cardiovascular adverse events — 8.1% with antihypertensives (or more aggressive regimens) vs 8.7% (with placebos or less aggressive regimens), which is a relative risk reduction of ~7%.^{216,217} A secondary outcome, all-cause death, however did not show any differences between these groups.

In other words, despite these marginal improvements in terms of decreased cardiovascular events and negligible impact on survival from antihypertensive medications, the FDA indicated that even their worst case scenario for increased cancer risk due to the exposures to NDMA in VCDs were even more miniscule in comparison to the health risks of not taking these blood pressure medications.

FDA also recognized that the valsartan manufacturers had no reason to test for the NDMA impurity previously:

“Because it was not anticipated that NDMA would occur at these levels in the manufacturing of the valsartan API, manufacturers would not have been testing for it. They would not have records that help identify this issue during an inspection. So this particular risk would not have been identified on an inspection.”

The impressions that these statements make are first, that NDMA at these trace levels are unlikely to be significant. Second, they indicate that in order to successfully test for a given impurity in API, manufacturers would need to be aware that NDMA could be present in the first place. Third they indicate that even at that point (August 2018), FDA was not entirely sure how NDMA was forming, even after investigating the process in great detail.

On May 2, 2018, FDA posted laboratory test results showing NDMA levels in recalled valsartan products, and the table was most recently updated on 5/2/19 and now includes NDEA level information.²²¹

Company	Product (tablets)	Lots Tested	NDMA level (micrograms - mcg/tablet)	NDEA level (micrograms - mcg/tablet)
Aurobindo Pharma Ltd	Amlodipine 10mg/Valsartan 320 mg	VKSA18005-A, VKSA18007-A, VKSA18001-A	Below LOD	0.02-0.09

Aurobindo Pharma Ltd	Valsartan 320mg	VUSD17008-A, VUSD17001-A, VUSD17009-A	Below LOD	0-0.05
Aurobindo Pharma Ltd	Valsartan 320mg/HCT 25mg	HTSB18001-A, HTSB18028-A, HTSB18029-A	Below LOD	0.02-0.19
Hetero Labs Ltd	Valsartan 320mg	VLS18049, VLS18051, VLS18050	0.33-0.44	Below LOD
Mylan Pharmaceutical Inc.	Amlodipine 10mg/Valsartan 320 mg	3079709, 3077618, 3079708	Below LOD	0.04-0.11
Mylan Pharmaceutical Inc.	Amlodipine 10mg/Valsartan 320 mg/HCT 25mg	2008702	Below LOD	0.05
Mylan Pharmaceutical Inc.	Valsartan 320mg	3080009, 3080010, 3079205	Below LOD	0.07-0.16
Mylan Pharmaceutical Inc.	Valsartan 320mg/HCT 25mg	3084886, 3093804, 3084862	Below LOD	0.20-0.38

Prinston Pharmaceutical	Valsartan 320mg	344B18027, 344B18028, 344B18029	15.18-16.30	Below LOD
Prinston Pharmaceutical	Valsartan 320mg/HCTZ 25mg	611B18025, 611B18026, 611B18027	13.18-20.19	Below LOD
Teva Pharmaceutical	Amlodipine 10mg/Valsartan 320 mg	26X053, 26X054, 26X055, 26X051, 26X044, 26X048	Below LOD	0-0.03
Teva Pharmaceutical	Amlodipine 10mg/Valsartan 320 mg/HCT 25mg	22X045, 22X046, 22X047, 22X038, 22X041	Below LOD	0-0.03
Teva Pharmaceuticals	Valsartan 320mg	1240425A, 1247282M	7.92-16.55	Below LOD
Teva Pharmaceuticals	Valsartan 320mg/HCTZ 25mg	1217576M, 1217577M, 1217578M	6.94-10.35	0-0.77
Torrent Pharmaceuticals	Amlodipine 10mg/Valsartan 320 mg/HCTZ 25mg	BBX2E001, BBX2E002, BBX2E003	10.24-11.53	Below LOD
Torrent Pharmaceuticals	Valsartan 320mg	BV48D001, BV48D002	0.56-0.62	1.12-1.22
Torrent Pharmaceuticals	Valsartan 160mg	BV47D001	0.45	1.31

As this table reflects, in many lots of the VCDs at issue, there was no NDMA detected, while in other lots the NDMA levels per tablet were 6.94 to 16.55 ug. Similarly for NDEA, in some lots the levels were below the limits of detection while in others the range was 0-0.03 mcg/tablet.

On April 4, 2019, FDA issued a further statement: “FDA Statement on the agency’s list of known nitrosamine-free valsartan and ARB class medicines, as part of agency’s ongoing efforts to resolve ongoing safety issue”

“And while we’ve concluded through our risk assessments that the maximum possible exposure to nitrosamines (which are also known environmental contaminants and found in water and foods, including meats, dairy products and vegetables) in ARB medicines appears to be small, their presence in drug products is not acceptable.” (emphasis added)

“Patients should continue taking their medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option -- **even if they learn that their ARB medicine is recalled. The risk associated with abruptly discontinuing the use of these important medicines far outweighs the low risk that our scientists estimate to be associated with continuing the medicine until the patient’s doctor or pharmacist provides a safe replacement or a different treatment option.** We’re closely monitoring the supply of ARBs and will communicate any drug shortages promptly to the public. Today’s news, of the certainty and broad number of nitrosamine-free ARB medicines, is another positive step. Health care practitioners should familiarize themselves with alternative medicines that can be used to treat hypertension, heart failure or renal disease in case of shortages..” (emphasis added)²²²

On August 28, 2018, FDA issued a further statement “clarifying the risk and scope of exposure”

“Clarifying the risk and scope of exposure

As part of our efforts to be transparent regarding impurities in ARBs, we want to make sure patients have a full understanding of how these impurities may affect them. **Notably, we would like to stress that the actual risk to patients is likely much lower than our estimates, which reflect a scientific assessment of the highest possible exposure.** We initially estimated that if 8,000 people took the highest valsartan dose (320 mg) containing N-Nitrosodimethylamine (NDMA) from the recalled batches daily for four years, there may be one additional case of cancer over the lifetimes of those 8,000 people. **In reality, the vast majority of patients exposed to NDMA through ARBs received much smaller amounts of the impurity than this worst-case scenario, and, since not all ARBs are affected, it’s very likely that a patient taking an ARB for four years would not have always received one of the affected products.**” (emphasis added)²²³

The impressions that these statements make are first, that NDMA at these trace levels are unlikely to be significant to patients, and that there would be a number of patients thinking they were exposed to lots with impurities, but that many would not have been, and therefore not at any increased risk of any harm.

In the course of its investigation of the nitrosamine impurity, FDA published what it considered to be acceptable limits of NDMA and NDEA exposure, reflecting the scientific evidence that people routinely are exposed to varying levels of NDMA and NDEA in food, water, air, cosmetics, and through endogenous formation.²²²

Interim Limits for NDMA and NDEA in Angiotensin II Receptor Blockers (ARBs)

Drug	Maximum Daily Dose (mg/day)	Acceptable Intake	Acceptable Intake	Acceptable Intake	Acceptable Intake

		NDMA (ng/day)*	NDMA (ppm)**	NDEA (ng/day)*	NDEA (ppm)**
Valsartan	320	96	0.3	26.5	0.083
Losartan	100	96	0.96	26.5	0.27
Irbesartan	300	96	0.32	26.5	0.088
Azilsartan	80	96	1.2	26.5	0.33
Olmesartan	40	96	2.4	26.5	0.66
Eprosartan	800	96	0.12	26.5	0.033
Candesartan	32	96	3.0	26.5	0.83
Telmisartan	80	96	1.2	26.5	0.33

“* The acceptable intake is a daily exposure to a compound such as NDMA or NDEA that results in a 1:100,000 cancer risk **after 70 years exposure**. (emphasis added to remind that this is the risk to increase cancer in 1 person per 100,000 over 70 years of continuous exposure at this level)

** These values are based on a drug's maximum daily dose as reflected in the drug label. For comparison with the levels of NDMA found in some common foods, please see our Aug. 20, 2018, update.”

In publishing these “limits”, FDA specifically referred the public to context provided by the a table setting forth the amounts of NDMA present in example food items. The table referenced, published on August 20, 2018, states that “NDMA is a known environmental contaminant. For context, it is found in water and foods including meats, dairy products and vegetables.” It presented an “Estimated Range of Daily NDMA Consumption for certain foods (Recommended daily food consumption rates based on Dietary Guidelines for Americans 2015-2020):

- Cured meat - 0.004-0.23 micrograms
- Smoked meat - 0.004-1.02 micrograms
- Grilled meat - 0.006-0.13 micrograms
- Bacon - 0.07-0.09 micrograms²²²

This table makes clear that NDMA exposure is a routine part of human life. Indeed, as set forth below, estimates for total dietary NDMA consumption often exceed the FDA’s suggested “acceptable intake.” Accordingly, to truly assess whether VCDs containing the NDMA impurity pose an increased risk of cancer at the levels tested in VCDs and over the duration

during which the impurity existed, it is critical to look at epidemiologic and other data concerning NDMA.

While I understand that other experts offered in this litigation will provide detailed opinions and a comprehensive review of the epidemiologic data at issue, I have reviewed the reports submitted by Plaintiffs' experts and the studies cited therein, as would be typical in my practice and for others in my field, and I feel compelled to provide commentary on some of the obvious limitations of the data on which they have relied and the ways in which the opinions proffered are not and cannot be supported by the data.

11. Epidemiologic Data Does Not Support Any Increased Risk of Cancer Caused by Ingestion of NDMA at the Levels Detected In Valsartan Containing the NDMA Impurity.

As set forth above, I have been asked to opine on whether there is sufficient data to support the conclusion, advanced by some of the plaintiffs' experts in this litigation, that, to a reasonable degree of medical certainty, ingestion of NDMA at the trace levels detected in some valsartan drugs could have caused the cancers that the plaintiffs have alleged in this litigation. It is my opinion that the data do not support that conclusion.

Any assessment of data concerning whether a particular exposure causes an effect under investigation needs to begin with and place the most weight on epidemiologic data that actually studies the relationship between the exposure (here, valsartan containing the NDMA/NDEA impurity) and the effect (cancer).

There are a few direct examinations of this relationship in the medical literature and my analysis begins with them. Plaintiffs' experts misguidedly focus their attention extensively on less valuable dietary nitrosamine studies and animal studies on nitrosamines which, as I explain below, are only weakly related to the inquiry at issue.

11a. Epidemiologic Data on Valsartan Do Not Support a Causal Association Between Exposure to NDMA in Valsartan and Cancer Risk

There have been two large cohort studies of individuals known to have filled prescriptions for valsartan produced by manufacturers in which the NDMA impurity was identified. Those studies compared individuals who took valsartan known or presumed to contain the NDMA impurity and individuals who took valsartan not believed to contain the impurity; the studies looked specifically at the rates of cancer in each cohort and found no statistically significant differences in cancer incidence among the two groups (with the exception of a possible association with hepatobiliary cancer, in one of the studies, discussed further below). This is the most valuable epidemiologic data that exists on this issue.

In 2018, Dr. Pottgard and his colleagues examined the potential risk of cancer for individuals exposed to valsartan products potentially containing the NDMA impurity compared to individuals who took valsartan products not believed to contain that impurity.²²⁴ The study subjects were identified from the national Danish registry between September 2011 and June 2017. No statistically significant associations were reported between valsartan products potentially containing NDMA and any type of cancer, the primary endpoint (HR 1.09 [0.85-

1.41] with 302 events). In subgroup secondary analyses by cancer type, there was no individual cancer that had a statistically significant association of valsartan products potentially containing the NDMA impurity. This study has strengths including the use of a high quality nationwide registry, therefore limiting selection bias. It also used drug dispensing data rather than prescription data, limiting bias due to non-adherence. The study also appropriately categorized subjects to limit immortal time bias. So while the study was somewhat limited by a relatively short follow-up time (median 4.6 years), this peer-reviewed study, designed to look for any association between valsartan use and cancer, found none — i.e. no association between valsartan containing the NDMA impurity and any cancer. Moreover, comparison of cancer incidence between those patients who were taking valsartan at the study time frame onset (prevalent users) versus those initiating valsartan during the time frame did not show that longer duration of treatment was associated with any higher cancer risk, suggesting that longer term follow up would not increase cancer risk later as opposed to earlier.²²⁴

In 2021, Dr. Gomm and his colleagues conducted a second but similar study comparing more than 400,000 patients who had taken some valsartan containing the NDMA impurity against 371,688 patients who had never been exposed to valsartan containing the NDMA impurity.²²⁵ The strength of this study is that all patients evaluated were taking valsartan. Also, all subjects had filled at least one prescription for valsartan during the period 2012 to 2017.¹ Whether a subject was exposed to potentially NDMA-containing valsartan was determined by detailed information from the manufacturers reflecting which batches of valsartan were produced by manufacturers whose product(s) were shown to contain the impurity (i.e. ZHP). Given the very large size of the study population, this study was well-powered to detect any association between NDMA-containing valsartan and increased cancer risk. However, no such association was observed overall (adjusted HR 1.01, 95% CI [0.99-1.03]). In other words, taking NDMA-containing the valsartan impurity was not associated with any increased risk in overall cancer or with any specific cancer. The analysis of individual cancer types, did show a slight statistically significant association, but not causation, between potentially NDMA-containing valsartan and liver cancer (adjusted HR 1.16 [1.03; 1.31], $p = 0.017$) but not for any other cancer evaluated (bladder, breast, colorectal, kidney, lung, melanoma, pancreas, prostate, nor uterine cancers). Importantly, there was no dose-dependent effect on the risk of liver cancer found for higher exposure to potentially NDMA-containing valsartan. Long term use (3-year) was not statistically significantly associated with liver cancer either. The authors conclude that their data is consistent with the Danish cohort, and much larger. However, the primary difference in the two studies of the findings of an association between NDMA-containing valsartan in liver cancer is notable that there were no cases of liver cancer detected at all among persons who had received potentially NDMA-containing valsartan in the Danish study. With multiple testing that has been conducted between the two studies, including for each of the various cancers, there is potential that a positive finding here in Gomm et al is due to mere chance, and further analysis is warranted to derive firm conclusions. Also, a limitation in these observational studies is that without randomization, despite attempt at adjustment of potential influencing factors, residual confounding cannot be entirely excluded.

¹ Notably, by examining all individuals who filled valsartan prescriptions, this study also more closely models the real world exposure and experience of valsartan users to the NDMA impurity, as opposed to FDA's "worst case scenario" analysis outlined above.

While each of these studies notes the obvious limitation of a somewhat shortened follow-up period, that period actually is more closely reflective of the plaintiffs in this litigation who claim their cancers similarly developed in a very short time period following their exposure to valsartan containing the NDMA impurity. Specifically, Pottegard et al. and Gomm et al. note that their studies were limited by the short follow-up time between the potential exposures and the assessment of cancer incidence (roughly 0-6 years, depending on the individual's exposure period), with median person-times follow up of 4.6 years (interquartile range 2.0-5.5 years) in Pottegard et al, and 3.25 years (interquartile range 2–4.75 years) in Gomm et al. But, the Plaintiffs in this litigation also claim to have been exposed to NDMA-containing valsartan and to have been diagnosed with cancer in a similarly short period after the exposure. As such, the Gomm and Pottegard studies are actually more closely analogous to the question at hand: whether the level and duration of potential exposure to NDMA from valsartan could have caused the cancers alleged in the short time period during which plaintiffs assert their diagnoses. The data from Gomm and Pottegard do not support that hypothesis.

In short, it is my opinion that the available epidemiological data does not support the hypothesis that exposure to NDMA-containing valsartan causes any excess cancer risk.

11b. Studies on NDMA in Diet and Enviroment Do Not Support an Association between Orally-Ingsted NDMA and the Cancers Alleged Here.

Of significantly less relevance to the present inquiry are the plethora of studies — relied upon heavily by plaintiffs' experts — which purport to examine a potential association between dietary nitrosamines and/or nitrosamine precursors (nitrite and nitrate) and the risk(s) of various cancers. For a number of reasons I will discuss throughout this section, those studies present flawed bases to draw conclusions about whether NDMA/NDEA-containing valsartan/VCDs could cause any of the cancers alleged in this litigation.

NDMA is one substance in a class of substances known as N-nitrosamines (or N-nitroso compounds). NDMA and/or nitrosamines are fairly ubiquitous chemicals found preformed in drinking water and some foods, in certain cosemtic and pharmaceutical products and through occupational exposures in certain industrial settings. As such, humans are exposed to exogenous (formed outside the body) nitrosamines such as NDMA every day in their diet and environment. Importantly, NDMA and other nitrosamines can also be formed endogenously (inside the body) by chemical reactions during the digestion of food containing nitrosamine precursors, such as nitrite and nitrate.^{226,227} Because humans are exposed to nitrosamines both endogenously and exogensouly, it is not possible to precisely and accurately measure the amount of nitrosamines or NDMA to which any one individual may be exposed on a daily basis.

Many studies have attempted to explore the effect of dietary (i.e. exogenous) nitrosamine consumption on cancer risk, but the results have been mixed and inconclusive. The studies I have reviewed regarding NDMA/nitrosamines and cancer, which have examined NDMA exposure in a variety of these kinds of exposures, do not show, through consistent, reliable data that NDMA presents an increased risk of cancer to humans.

For example, Dr. Choi and his colleagues conducted a cohort study which found a positive association between consumption of *precursors* of n-nitroso compounds and gastric cancer, based on a questionnaire of dietary history and estimated levels of n-nitroso compounds in the foods surveyed.²²⁸ The highest risk correlation was with consumption of smoked meats and fish; dietary NDMA was not measured. On the other hand, Chyou, et al., conducted a similar dietary history-based cohort study and found no association between dietary processed meats, dried fish and pickled vegetables and gastric cancer.²²⁹ Likewise, Dr. Jakszyn and colleagues conducted a series of studies examining a hypothetical link between dietary n-nitroso compounds and gastric cancer, bladder cancer, and prostate cancer.²²⁶ They did not find a positive association. In contrast, Dr. Keszei and colleagues conducted a study finding positive association between dietary NOCs and esophageal and other gastric cancers.²²⁷

As noted above, each of these studies is inherently limited in its utility, because it is based on estimated levels of nitrosamines or even nitrosamine precursors in diet; such a study design is obviously much more attenuated from the instant question of whether NDMA in valsartan/VCDs causes cancer than the direct epidemiological studies I describe above.

One of the biggest impediments in the reliability of this data is the question of how to measure accurately the amount of NDMA/nitrosamines that any individual or population might be exposed to. For example, with regard to dietary exposures, most studies try to obtain this information through “food-frequency questionnaires.” These devices are recognized as being imprecise if not unreliable, in that they depend on study participants recalling accurately which foods they consumed and the quantify of such foods, particularly those foods that are considered potential sources of NDMA.^{230,231}

Even if study subjects in a nutritional epidemiologic study recall this kind of information accurately, how much NDMA might be in any particular food product, is usually not precisely known. These studies rely on published literature or databases which are not necessarily reliable or accurate. As one study noted: “It is difficult, however, to estimate the N-nitrosodimethylamine intake of individuals based on questionnaire and published data on N-nitrosodimethylamine contents of food. The nitrosamine contents of food vary across countries and over time, because of changes in methods of food processing, and available data are limited for some food items... food-frequency questionnaires are prone to the misclassification of dietary intake...”²²⁷

Importantly, however, some studies have attempted to estimate the total dietary intake of NDMA and/or N-nitrosamines. One researcher estimated that his study population consumed .123 µg/day of NDMA daily, from food and beer.²³² Another calculated the 75th percentile intake of NDMA among study participants at .51 µg/day; a third calculated the highest consumption group as averaging .179 µg/day.^{233,234} These results reflect the significant variability in estimating NDMA in diet; they also show that adults may consume far more NDMA through diet alone than the amount FDA has deemed a safe daily exposure.

Notably, that figure does not account for any endogenously formed NDMA to which we are exposed. Some studies have estimated that endogenously formed NDMA/nitrosamines account for between 45%-75% of total exposure; some estimates have been even higher.^{226,235} Dr.

Jakszyn and colleagues concluded that endogenous exposure (i.e. exposure to chemicals synthesized in the body) is “probably the major contributor to the overall burden of human exposure to NOCs [nitroso compounds].” They estimated that study participants were exposed to 93 µg/day on average from endogenously formed NOCs, as compared against less than 1 µg/day from exogenous sources.²²⁶ Frischi et al., while noting the difficulty of estimating the amounts of endogenously formed NDMA, calculated a level of .37 µg per gram of nitrate/nitrite rich foods consumed.²³⁵ They also noted a series of studies (Groenen, 1980; Sen, 1985; Krul 2004) which reported endogenous formation of NDMA up to 44 µg *per portion* of amine-rich food (e.g. cheeses/dairy, meat/fish). Similarly, Hrudey et al. (2013) analyzed NDMA levels blood samples, levels of the DNA adduct caused by NDMA (O⁶-methylguanine) and urinary excretion of NDMA and estimated endogenous NDMA formation between 4 µg/kg/day and 220 µg/kg/day. Under those estimates, a 100kg person would be exposed to between 400 and 22,000 µg of endogenously-formed NDMA daily.²³⁶

Those studies’ estimates suggest that, even under an FDA’s “worst case scenario” model of the highest daily exposure possible for the longest time possible of NDMA-containing valsartan, humans are exposed to far more endogenously-formed NDMA. Clearly, many people are exposed to well over the FDA’s recommended limit of NDMA on a daily basis, throughout the majority of their lives.

Confounding is another concern that permeates many of these dietary nitrosamine studies. For example, in De Stefani 1998, the study investigators reported a statistically significant association between dietary NDMA and gastric cancer. However, in a follow-up study in the same population but subsequent years (De Stefani 2001), the authors repeated the analysis and found the association was no longer significant when adjusting for additional confounding factors -- total energy intake and intake of proteins and total fat -- which had not been considered in the earlier study. Similarly, Goodman, et al. conducted a study of high fat.²³⁷ Dr. Goodman and his colleagues concluded that high dietary nitrosamine intake is associated with an increased risk for lung cancer; but, the study authors conceded that the association was strongest in men who were heavy smokers, which is clearly a significant confounder. Confounding in nutritional epidemiology is particularly a problem given the number of dietary components in each food item and the diet in general.

Multiple comparisons is another reason that significant associations that really occur by chance alone rather than a true association can compromise the results of studies examining potential dietary risk factors.²³⁸

Overall, the findings on dietary NDMA and cancer risk are mixed – some studies report a statistically significant association (typically in the group with the highest exposure), while other studies do not. Most of the statistically significant findings are reported in case-control studies and have not been sufficiently replicated in cohort studies. Prospective cohort studies are considered superior to case-control studies in nutritional epidemiology.

There are many limitations to these studies and in general, bias, confounding, and chance cannot be ruled out as likely explanations for the findings.

11c. Studies of Occupational Exposures to NDMA Do Not Support an Association between Orally-Ingested NDMA and the Cancers Alleged Here

Plaintiffs' experts (in particular Dr. Etminan) rely heavily on one study concerning NDMA exposures in an industrial setting. Specifically, Hidajat, et al. (2019) examined NDMA exposure in the UK rubber industry and reported statistically significant increased risks between NDMA and mortality from all cancers combined, bladder, brain, esophagus, leukemia, liver, lung, multiple myeloma, non-Hodgkin's lymphoma, pancreas, prostate, and stomach cancers. Laryngeal cancer mortality was the only cancer with non-statistically significant association.²³⁹

This study, however, had numerous limitations and confounders, many of which Dr. Etminan uses as the bases for his own criticisms of other studies cited in this report. Among other things, Hidjat et al. noted that rubber industry workers are exposed to numerous carcinogens, including N-nitrosamines, rubber (process) dust, rubber fumes, polycyclic aromatic hydrocarbons including phthalates, aromatic amines including β -naphthylamine and solvents including benzene; as they state, "disentangling exposure-response associations between specific suspected carcinogens and cancer risk in this industry remains difficult." Critically, all the exposure considered in this study was by inhalation. That different route of exposure implicates different metabolic pathways, different tissue exposures, and other factors. As a result, any results of a study addressing inhaled NDMA or other compounds is of limited utility in answering the question whether *orally ingested* NDMA could cause the cancers plaintiffs have alleged here. Moreover, the Hidjat study used estimations of NDMA exposure based on job title and air quality measurements associated with those job titles, while also assuming study participants remained in the same position throughout their careers. That is a significant and, in my view, implausible assumption and makes the estimations inherently questionable. Finally, the Hidjat study made no effort to control for smoking history. Obviously, tobacco smoking is one of the most-studied carcinogenic exposures and is known to cause many of the cancers at issue here. Presumably the subjects in the Hidjat study — manufacturing employees in Britain beginning in the 1970s — have significant exposures to tobacco smoke, confounding all of the study's findings.²³⁹

Other occupational studies considered nitrosamines as a group. In a study of the German rubber industry, Straif 2000, reported on nitrosamines as a group (while noting that NDMA and NMOR, another nitrosamine were found in the highest concentrations) and found a statistically significant increased risks between nitrosamines and mortality from all cancers combined, lip/oral cavity/pharynx cancers combined, and esophageal cancer.²⁴⁰ Additional studies have reported on occupational exposure to nitrosamines (without any specific mention of NDMA) and cancer incidence or cancer mortality. No association was found for occupational exposure to nitrosamines and incidence of pancreatic cancer²⁴¹, stomach cancer^{238, 242} or stomach cancer mortality.²⁴³ Cocco 1998 found no association between occupational exposure to nitrosamines and gastric cardia cancer mortality. A follow-up study using the same methods²⁴⁴ reported an association (unadjusted) between occupational exposure to nitrosamines and gastric cancer, although the association lost significance with further adjustment of confounders.

In sum, as with the dietary NDMA studies, these studies also suffer from multiple limitations, particularly with regard to the issues in this case. NDMA (or nitrosamine) exposure in an industrial or occupational setting is by predominantly by inhalation rather than by ingestion. In addition, most studies evaluated nitrosamines as a group rather than NDMA specifically and evaluated cancer mortality rather than cancer incidence. And, like the dietary NDMA studies, these study authors make many assumptions to estimate exposure levels which may or may not be accurate. Moreover, the study authors are unable to eliminate confounding as an issue, since in many of the reports the study authors did not adjust for other occupational exposures, for smoking, or for other factors. As such, much less weight can be given to these studies than to direct epidemiological evidence that looked at NDMA-containing valsartan. I give little weight to this evidence and could not rely on it to render any opinions about carcinogenesis that were offered to a reasonable degree of medical certainty.

11d. NDMA Animal Studies

In the expert reports I have reviewed from the plaintiffs' experts, there are several references to animal studies on the carcinogenic potential of NDMA. *E.g.*, Etminan Report at p. 22; Lagana Report at p.32; Panigrahy report at p. 35. While those studies, broadly speaking, have demonstrated that NDMA is carcinogenic to several animal species, they do not serve as a meaningful basis to infer carcinogenicity in humans, particularly at the dose levels in this litigation.

Plaintiffs' experts focus extensively on the study by Peto, et al. (1991) concerning NDMA's carcinogenesis in rats.^{245,246} In that study, the researchers administered doses up to 840 µg/kg/day – doses approximately 8,750x the .096 µg limit established by FDA. While the authors concluded that NDMA was carcinogenic to the rats and observed a dose-response relationship, they found lifetime liver cancer incidence above the background rate in the control group rats only at doses above 0.3 ppm. Expressed in micrograms, that dose equates to 15 µg/kg/day. For a 100kg human, that would mean 1,500 µg of NDMA, daily, or more than 75 times the amount of NDMA found in any valsartan product, daily for a lifetime. The significantly higher doses used in the Peto et al. study demonstrates why it is inherently unreliable to extrapolate that data to human carcinogenesis.

Other studies, also directly address the limited utility of the Peto et al. data when one attempts to extrapolate it to human carcinogenicity. As one study put it: "Extrapolation of rodent carcinogenesis data to man is particularly difficult because of known species differences in metabolic pathways (both activation and detoxification), involving potentially carcinogenic chemicals."²⁴⁷

On the other hand, while animal studies are of limited utility in extrapolating data to draw firm conclusions about human carcinogenesis, none of the animal studies relied upon by Plaintiffs' experts demonstrates that exposure to the levels of NDMA demonstrated to exist in certain valsartan medications would be capable of causing cancer when administered over the brief period that the impurity existed in those medications.

Indeed, animal studies on the carcinogenicity of a broad range of nitrosamines in nonhuman primates have reached precisely the opposite conclusion. Adamson, et al., studied nitrosamine carcinogenesis in non-human primates, because those animals “may provide a more suitable model for the study of potential carcinogens, particularly those requiring metabolic activation.” It is well known that NDMA requires metabolization by a specific cytochrome enzyme that only exists in certain human tissues. Studying the more closely analogous monkeys, Adamson et al. stated: “The nitroso compounds as a class appear to be potent carcinogens in nonhuman primates; all but one of these compounds (*N-nitrosodimethylamine*) have induced tumors in monkeys... four of the six monkeys treated with bimonthly intraperitoneal (ip) injections of NDMA (10 mg/kg) have been necropsied, and none have developed tumors.” In other words, in a direct study of NDMA’s carcinogenicity in monkeys, injections of **10 mg/kg** of NDMA — a level far, far, above that demonstrated to exist in valsartan — failed to cause tumorigenesis.²⁴⁷

In those same studies, the “apparent cumulative carcinogenic dose” of NDEA required to induce cancer was 1.4 grams. As set forth above, the highest measured level of NDEA in any valsartan medication was 1.3µg (Torrent – 160mg). In other words, Adamson et al. found that no dose of NDMA induced cancer in monkeys and that a cumulative dose of NDEA more than one million times that present in any valsartan pill was the carcinogenic dose.

The authors also noted that the dose response in monkeys was not linear: “The tumors developing in the six animals receiving the 5-mg/kg dose required a latent period of 65 months, a figure that shows a marked deviation from the value (42 months) expected if the relationship between dose and latent period is indeed linear.” *Id.*

Similarly, Takayama et al. studied chemical carcinogenesis in non-human primates and found that, when 7 monkeys were treated with 7.25mg/kg of NDMA daily (for a cumulative dose of 7 grams), none died of malignant tumors.²⁴⁸

Berger, et al. studied the carcinogenicity in rats of administration of combinations of nitrosamines, including, relevantly, administration of .1mg/kg of NDEA. Among other things, the authors noted that esophageal cancer incidence fell from 26% to not detectable levels, when the dose of NDEA was reduced from .1mg/kg to .032 mg/kg.²⁴⁹ Noting that this result differed from the results obtained by Peto et al., the authors hypothesized that differences in the rat species used between the two studies might account for these differences in dose-response relationship. Such a hypothesis underscores the limited utility of linear extrapolation from rats to humans.

Taken together, animal studies that have evaluated the carcinogenicity of NDMA depend on the species studied, doses administered and the duration of exposure. While one rat study concluded that NDMA was carcinogenic and demonstrated a dose response relationship, this was at exceedingly high doses far higher than the limit established by the FDA. Another rat study with a different rat species did not find such relationships. In a more representative species, non-human primates, studies failed to demonstrate NDMA to be carcinogenic even at doses far higher than the trace levels found in VCDs, and also found a non linear dose response

relationship with NDEA. As such, the totality of the animal data, for which I put more emphasis on non-human primate models, suggest the trace levels found in VDCs are not carcinogenic.

12. Summary of Epidemiological, Diet, and Toxicologic Data and Conclusion

It is my opinion, to a reasonable degree of medical and scientific certainty that, considered together, the available epidemiological data, the dietary studies, and the animal studies do not support the hypothesis that exposure to NDMA and/or NDEA-containing valsartan at the levels observed in those drugs and over the duration that those impurities were understood to exist could cause any excess cancer risk (including, specifically, esophageal, gastric, pancreatic, liver and colorectal/intestinal, lung, pharyngeal cancers, bladder, kidney, prostate, uterine, breast, nor hematologic (blood) cancers). Indeed, there is no reliable scientific data that supports the such a hypothesis — i.e. that exposure to valsartan/VCDs containing an NDMA and/or NDEA impurity at the levels observed causes any increased cancer risk. The other risk factors associated with those cancers are many and (along with the natural process of aging) are much more likely to have played a role in the development of any particular plaintiff's cancer than exposure to trace amounts of NDMA and/or NDEA in valsartan/VCDs.

It is likewise my opinion, to a reasonable degree of medical and scientific certainty, that there is no medically justifiable reason to require extra or early cancer screening or enhanced medical monitoring for patients believed to have been exposed to the trace amounts of NDMA and/or NDEA understood to exist in certain batches of valsartan drugs. These opinions are based on based on my training and experience and review of materials and literature, including but not limited to those listed on Exhibit B.

I reserve the right to modify this report and my opinions herein as additional information is provided to me, including but not limited to additional records and the depositions of Plaintiff's experts which are ongoing. I further reserve the right to use at trial any exhibits as a summary or in support of all of my opinions including: (1) any of the materials, or excerpts identified in this report and attachments, including the materials considered list; (2) excerpts from scientific articles or learned treatises; (3) demonstrative models; (4) exhibits used by Plaintiffs' experts, or other witnesses; (5) any exhibit used in or identified at any deposition taken in this litigation. If further data becomes available, I will be happy to review it and consider whether to modify any portion of these opinions.

Best Regards,

Daniel Catenacci, MD
Associate Professor of Medicine
Director of Gastrointestinal Oncology
Assistant Director of Translational Research, Comprehensive Cancer Center
University of Chicago Medicine & Biological Sciences
773 702 7596

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[%20FDA%20presents%20interim%20limits%20of,%20%200.33%20%204%20more%20rows%20](#)
20 Last accessed 7/17/2021

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A handwritten signature in black ink, appearing to read 'DC' followed by a stylized flourish.

Dated: August 27, 2021

Daniel Catenacci, M.D.

CATENACCI

EXHIBIT A

DANIEL VIRGIL THOMAS CATENACCI, M.D.

March, 2021

PERSONAL**Office Address:**

5841 S. Maryland Ave MC2115
Chicago, IL, 60637
Office (773) 702-7596

Place of Birth: Sarnia, Ontario, Canada
Citizenship: Canadian, U.S. Permanent Resident
E-mail: dcatenac@medicine.bsd.uchicago.edu

EDUCATION:

1995-1999 Honors Bachelor of Science, BSc. University of Waterloo, Waterloo, Ontario, Canada.
1999-2003 Doctor of Medicine, MD. Wayne State University, Detroit, Michigan.
2011-2014 Master of Science in Health Studies, MSc University of Chicago, Chicago, Illinois.
Biostatistics, Clinical & Translational Investigation.

POSTDOCTORAL TRAINING:

2003-2006 Internal Medicine Intern/Resident
UCLA Medical Center, Los Angeles, California
2006-2007 Clinical Fellow, Medical Oncology/Hematology
University of Chicago Medical Center, Chicago, Illinois.
2007-2010 GI Translational Research Fellow, Digestive Malignancies Laboratory
PI: Ravi Salgia. University of Chicago Medical Center, Chicago, Illinois.

POSTDOCTORAL EDUCATIONAL WORKSHOPS:

2007 AACR "Molecular Biology in Clinical Oncology" Workshop
Given Institute of the University of Colorado, Aspen, Colorado. July 1-7
2007-2008 Clinical Research Training Program, Essentials of Patient Oriented Research (EPOR I)
University of Chicago Medical Center, Chicago, Illinois. **Fall & Winter**
2008 Summer Workshops in Molecular Biology, New England Biolabs
Smith College, Clark Science Center, Northampton, MA. July 6-19.
2008 ECCO-AACR-ASCO "Methods in Clinical Cancer Research"
Flims, Switzerland, June 21-27.
2017 AAI "Advanced Course in Immunology" Boston, MA. July 23-28.

ACADEMIC APPOINTMENTS

2010-2012 Instructor, Department of Medicine, Section of Hematology/Oncology, University of Chicago, IL
2010- Member, Comprehensive Cancer Research Center, University of Chicago, IL
2012-2018 Assistant Professor, Department of Medicine, Hematology/Oncology, University of Chicago, IL
2016-2018 Associate Director, Gastrointestinal Oncology Program
2018- Director, Interdisciplinary Gastrointestinal Oncology Program
2018- Assistant Director, Translational Research, Comprehensive Cancer Center
2019- Associate Professor, Department of Medicine, Hematology/Oncology, University of Chicago, IL

HOSPITAL APPOINTMENTS

2010- Attending Physician. University of Chicago Medical Center, Chicago, IL.

LICENSURE AND CERTIFICATION:

Licensed to practice medicine:

05/2005-2009 California: #A91242
07/2006- Illinois: #036-115556

American Board of Internal Medicine:

2006-2016 Internal Medicine
2009-2029 Medical Oncology (Hematology: board eligible)

Daniel Catenacci, M.D.

PROFESSIONAL MEMBERSHIPS and ACTIVITIES:

1999-2003	American Medical Association
2003-2004	American College of Physicians
2002-	The Pharos, Alpha Omega Alpha AQA quarterly
2005-	Medical Council of Canada
2006-	American Society of Clinical Oncology, Associate Member
2006-	American Society of Hematology, Associate Member
2007-	American Association for Cancer Research, Associate Member
2010-	Associate Investigator Pharmacogenomics and Experimental Therapeutics
2010-	University of Chicago Comprehensive Cancer Center Member
2013-	American Gastroenterological Association, Associate Member
2015-	Overseas Fellow of the Royal Society of Medicine, United Kingdom
2016-	European Society of Medical Oncology, Associate Member

HONORS AND AWARDS:

1995-1999 University of Waterloo, Waterloo, Ontario, Canada, (Undergraduate):

- Dean's Honors List, Undergraduate Year I to Year IV.
- Nominated for the Governor General's Silver Medal and Alumni Gold Medal for highest academic standing in Faculty of Science, 1999
- Recipient of Sony of Canada Science Scholarship for highest academic standing, Faculty of Science, University of Waterloo, 1998

1999-2003 Wayne State University School of Medicine, Michigan (Medical School):

- Honors with Highest Distinction (*Summa Cum Laude*), Years I to IV.
- *Alpha Omega Alpha* AQA Honor Medical Society, Inducted Yr II, 2001

1999-2003 Harvard Medical School/Harvard Institute of Medicine (Medical School):

- William F. von Liebig Summer Research Fellowship, Summer, 2000

2003-2006 UCLA Medical Center (Residency):

- Distinguished Teacher Award for UCLA Interns and Medical Students, 2004-2006

2006-2010 University of Chicago Medical Center (Fellowship):

- ASCO 2009 Young Investigator Award (YIA), 07/2009-06/2010.
- Amgen Hematology & Oncology Fellowship Grant Support Program, 04/2008-03/2009

2010-2012 University of Chicago Medical Center (Instructor):

- Cancer Research Foundation Young Investigator Award (CRF YIA). 10/2010-09/2011.
- K-12 Scholar. Paul Calabresi Career Development in Clinical Oncology. 10/2010-09/2013.
- NCI/CTEP Career Development LOI Awarded – A Randomized Discontinuation Trial of OSI-906 in metastatic Colorectal Cancer After Two or More Lines of Prior Therapy 10/29/2010.

2012-2018 University of Chicago Medical Center (Assistant Professor):

- ALLIANCE for Clinical Trials in Oncology Foundation Young Investigator Award 07/2012-06/2013
- Esophago-Gastric NCI Task Force, ALLIANCE New Investigator (06/2012-11/30/17)
- Best Abstract and Oral Presentation at the 5th Annual WIN (Worldwide Innovative Networking in Personalized Cancer Medicine) Symposium. July 7-10, 2013. Paris, France.
 - Towards personalized treatment for gastroesophageal adenocarcinoma: strategies to address inter- and intra- patient tumor heterogeneity: PANGEA
- Best Abstract Translational Research Faculty Category Annual Janet Rowley Research Day University of Chicago, March 4, 2014 PANGEA Clinical Trial Design and Pilot results.
- K23 Scholar Awarded 9/2014-8/2017.
- Named on the "Chicago's Top Cancer Doctors' List. December, 2016
- Tree of Life Medical Award. Debbie's Dream Foundation for Stomach Cancer. April, 2018

2019- University of Chicago Medical Center (Associate Professor):

CLINICAL

I am an adult Medical Oncologist with sub-specialization in Gastrointestinal Cancers, with focus on upper GI cancers, and special interest in Esophagogastric adenocarcinoma and Cholangiocarcinoma/Gallbladder cancer.

2010- GI Oncology Clinic (1 day/week, 12 months/year, **30% effort**)

2010- Inpatient Service - Chemotherapy service, Housestaff Supportive Oncology (4 weeks/year, **10% effort**)

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SCHOLARSHIP:

BIBLIOGRAPHY:

Peer Reviewed Articles:

Original Articles

1. Zhang W, **Catenacci DVT**, Duan S, Ratain MJ. A Survey of the Population Genetic Variation in the Human Kinome. *J of Hum Genet.* Aug;54(8):488-92. 2009. PMID 19644514.
2. **Catenacci DVT**, Cervantes G, Yala S, Nelson EA, El-Hassani E, Kanteti R, El Dinali M, Hasina R, Brägelmann J, Seiwert T, Sanicola M, Henderson L, Grushko T, Olopade O, Karrison T, Bang YJ, Kim WH, Tretiakova M, Vokes EE, Frank DA, Kindler HL, Huet H, Salgia R. RON (*MST1R*) is a novel prognostic marker and therapeutic target for gastroesophageal adenocarcinoma. *Cancer Biol Ther.* 12:1, 1-38, July 1, 2011. PMID 21543897. **Featured Article**.
3. **Catenacci DVT**, Henderson L, Xiao SY, Priti Hegde, Premal Patel, Robert L. Yauch, Peterson A, Salgia R. Durable complete response of gastric cancer with anti-MET therapy followed by resistance at recurrence. *Cancer Discov.* 2011 Dec 1;1(7):573-579.PMID: 22389872.
4. Kanteti R, Krishnaswamy S, **Catenacci DVT**, Cervantes G, Henderson L, Tan Y, El-Hassani E, Husain AN, Tretiakova M, Huet R, Salgia R. Differential Expression of RON in Small and Non-Small Cell Lung Cancers. Epub May24 *Genes Chromosomes & Cancer* 2012. PMID 22585712.
5. Shah MA, Wainberg ZA, **Catenacci DVT**, Hochster HS, Ford J, Kunz P, Lee FC, Kallender H, Cecchi F, Rabe DC, Keer H, Martin AM, Liu Y, Gagnon R, Bonate P, Liu L, Gilmer T, Bottaro DP. Phase II Study Evaluating 2 Dosing Schedules of Oral Foretinib (GSK1363089) in patients with Advanced or Metastatic Gastric Cancer. *PLoS One.* 2013;8(3):e54014. PMID:23516391
6. Geynisman DM, Zha Y, Kunnavakkam R, Aklilu D, **Catenacci DVT**, Polite BN, Rosenbaum A, Namakydoust A, Karrison T, Gajewski TF, Kindler HL. A randomized pilot phase I study of modified Carcinoembryonic antigen (CEA) peptide (CAP1-6D)/Montanide/GM-CSF-vaccine (CEA-vac) in patients (pts) with pancreatic adenocarcinoma (PC). *Journal for ImmunoTherapy of Cancer* 2013, 1:8. PMID pending
7. Ross JS, Wang K, Gay L, Al-Rohil R, Rand JV, Jones DM, Lee H, Sheehan CE, Otto GA, Palmer G, Yelensky R, Lipson D, Morosini D, Hawryluk M, **Catenacci DVT**, Miller VA, C Chaitanya, Stephens PJ. New routes to targeted therapy of intrahepatic cholangiocarcinomas revealed by Next Generation Sequencing. *Oncologist* 2014 Feb 21. PMID 24563076.
8. Salgia R, Patel P, Bothos J, Yu W, Bai S, **Catenacci DVT**, Peterson A, Ratain M, Polite B, Mehnert J, Moss R. Phase I dose-escalation study of onartuzumab as a single agent and in combination with bevacizumab in patients with advanced solid malignancies. *Clin Cancer Res.* 2014 Feb 27. PMID:24493831.
9. **Catenacci DVT**, Liao WL, Thyparambil S, Henderson L, Peng Xu, Rambo B, L Zhao, Hart J, Xiao SY, Bengali K, Uzzell J, Dafler M, Krizman D, Cecchi F, Bottaro D, T Karrison, Veenstra TD, Hembrough T, Burrows J. Absolute Quantitation of c-Met using Mass Spectrometry for Clinical Application: Assay Precision, Stability, and Correlation with *MET* gene amplification in FFPE Tumor Tissue. *PLoS One.* 2014 Jul 1;9(7):e100586. PMID:24983965.
10. **Catenacci DVT**, Amico A, Nielsen S, Geynisman D, Carey GB, Gulden C, Fackenthal J, Kindler HK, Olopade F. Tumor Genome Includes Germline Genome - Are We Ready For Surprises? *International Journal of Cancer* 2014 August 2014. PMID 25123297.
11. **Catenacci DVT**. Next-generation clinical trials: Novel strategies to address the challenge of tumor molecular heterogeneity. For: Molecular Oncology Special Edition on "Innovative clinical trials for development of personalized cancer medicine". *Molecular Oncology* October, 2014. PMID 25557400
12. Ali SM, Sanford EM, Klempner SJ, Robinson DA, Wang K, Palma NA, Chmielecki J, Yelensky R, Palmer GA, Morosini D, Lipson D, **Catenacci DVT**, Braithe F, Erlich R, Stephens PJ, Ross JS, Ou SH, Miller VA. Prospective Comprehensive Genomic Profiling of Advanced Gastric Carcinoma Cases Reveals Frequent Clinically Relevant Genomic Alterations and New Routes for Targeted Therapies. *Oncologist.* 2015 Apr 16. PMID 25882375

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13. **Catenacci DVT**, Chapman CG, Xu P, Koons A, Konda V, Siddiqui U, Waxman I. Acquisition of Portal Vein Circulating Tumor Cells in Pancreatobiliary Cancers by EUS Guided Portal Vein Sampling. *Gastroenterology* doi: 10.1053/j.gastro.2015.08.050. [Epub ahead of print] PMID: 26341722
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19. Sellappan S, Blackler A, Liao WL, O'Day E, Xu P, Thyparambil S, Cecchi F, Hembrough T, **Catenacci DVT**. Therapeutically induced changes in HER2, HER3, and EGFR protein expression for treatment guidance. *JNCCN* May 2016. 27160229
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21. An E, Ock CY, Kim TY, Lee KH, Han SW, Im SA, Kim TY, Liao WL, Cecchi F, Blackler A, Thyparambil S, Kim WH, Burrows J, Hembrough T, **Catenacci DVT**, Oh DY, Bang YJ. Quantitative proteomic analysis of HER2 expression in the selection of gastric cancer patients for trastuzumab treatment. *Annals of Oncology* 2016 Sep 29. pii: mdw442. PMID: 27687309
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26. Bendell JC, Hochster H, Hart LL, Firdaus I, Mace JR, McFarlane JJ, Kozloff M, **Catenacci DVT**, Hsu JJ, Hack SP, Shames D, Phan SC, Cohn AL. Efficacy and safety results from a phase II randomised trial (GO27827) of first-line FOLFOX plus bevacizumab with or without onartuzumab in patients with metastatic colorectal cancer (mCRC). epub *The Oncologist*. PMID: 28209746
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Editorials/Commentaries:

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74. **Catenacci DVT**. A PERFECT biomarker-focused study of neoadjuvant IO for esophagogastric cancer. *Clin Can Res* 2021, in press

Reviews:

75. **Catenacci DVT**, Schiller GJ. Myelodysplastic Syndromes: A Comprehensive Review. *Blood Reviews* Nov 2005; 19(6):301-319. PMID: 15885860 **Top 20 cited in *Blood Reviews* towards the 2007 impact factor.
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Consensus Statements and Guidelines:

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Book Chapters:

93. **Catenacci DVT**, Cohen E., Villaflor V. Gastroesophageal Tumors: Principles and Practice. Chapter 33: Principles of Multimodality Therapy, pages 229-242. Mar 2009. (Edited by Jobe, Hunter and Thomas).
94. **Catenacci DVT**. Cancer Biology Review: A Case-Based Approach. Chapter 4: Cell Surface Receptors and Signal Transduction: Principles of Cancer Biology. 2014 (Edited by Stadler and Winters).
95. Polite BN, **Catenacci DVT**. ASCO Self Evaluation Program (SEP) 7th edition, Gastrointestinal Malignancies Chapter. 2021
96. Lin D, Khan U, Goetze TO, Reizine N, Goodman KA, Shah MA, **Catenacci DV**, Al-Batran SE, Posey JA. Gastroesophageal Junction Adenocarcinoma: Is There an Optimal Management? *Am Soc Clin Oncol Educ Book*. 2019 Jan. PMID: 31099690

Original Articles under revision, submitted or in preparation:

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1. **Catenacci DVT**, Chao J, Klemptner S, Janjigian Y, Kim R, Liepa A, Kuder C, Chin S, Shah M, Fuchs C. A Systematic Review of First and Second Line Randomized Controlled Trials for Advanced Gastroesophageal Adenocarcinoma: Towards a Treatment Sequencing Strategy. *Manuscript in Preparation*
2. Grewal NKS, Seritella A, Peterson B, Moya S, Del Gaudio D, Das S, Lui P, Klemptner S, Catenacci DVT. Assessment of FcgRIIIA single nucleotide polymorphisms on the efficacy of IgG1 monoclonal antibodies in patients with advanced gastroesophageal adenocarcinoma. *Manuscript in Preparation*
3. **Catenacci DVT**, Karrison T, Dignam J, Ji J. Statistical considerations of the 'Expansion Platform Clinical Trial Design Type II'. *Manuscript in preparation*.
4. Reizine N, Peterson B, Moya S, Wang S, Kanteti R, Tan YHC, Catenacci DVT. Targeted therapies for targeted populations: Met inhibition for *MET* amplified gastroesophageal adenocarcinoma. AMG DN Merck Serono TL *Manuscript in Preparation*
5. Reizine N, Veneris JT***, Peterson B, Moya S, Wang S, Tan YHC, Eng OS, Turaga K, Catenacci DVT. Targeted therapies for targeted populations: FGFR inhibition for FGFR2 amplification and/or fusion as for gastroesophageal adenocarcinoma. *Manuscript in Preparation*

RESEARCH SUPPORT:

Current Grant Support:

SU2C: Early Detection and Interception of Diffuse and Intestinal Gastric Cancer. (Andrew Chan, MGH. Co-Principal Investigator, (2020-2023) (\$3 million, Catenacci 20% effort).

R01: Integration of genomic and phenotypic data for cancer research and clinical support. PI Yitan Zhu, Northshore. (2018-2023, Catenacci effort 10%)

General Research Fund: 2010-

Live Like Katie Foundation Award: 2013- (\$300,000, 10% effort)

Sal Ferrara Fund for PANGAEA Award: 2014- (\$300,000, 10% effort)

Castle Foundation Award: 12/31/16-12/31/2020 (\$250,000 over 4 years, 15% effort)

Submitted/Planned Submission, Pending Grant Support:

Submitted: P30: 2021 Cancer Clinical Investigator Team Leadership Award (CCITLA) 15% effort

Planned R01: Tumor Molecular and Immunologic Biomarker Heterogeneity in Gastroesophageal Adenocarcinoma. PI Catenacci 20% effort

Planned: R01: Targeting Wild-Type Amplified KRAS and GNAS in Gastroesophageal Adenocarcinoma. PI Catenacci 20% effort

Past Grant Support:

Amgen Hematology & Oncology Fellowship Grant. "The Role of RON Receptor Tyrosine Kinase in Gastroesophageal Cancers" (7/2008-06/2009).

CTSA-ITM Core Subsidies Fellow Grant. "Immunohistochemical Evaluation of The Role of RON and MET Receptor Tyrosine Kinases in Gastroesophageal Cancers" (1/09-06/09).

R21. "Novel Targeted Therapy in Pancreatic Cancer". Co-PI Salgia/Kindler (07/2009-06/2011).

ASCO 2009 Young Investigator Award. "The Role of RON (MST1R) Receptor Tyrosine Kinase in Gastroesophageal Cancers as a Therapeutic Target." (07/09-06/10).

Cancer Research Foundation Young Investigator Award (CRF YIA). "The Role of RON Tyrosine Kinase in Gastroesophageal Cancer". \$75,000 5% effort (1/2011-12-2011).

American Research and Recovery Act (ARRA) NCI 8418. "GDC-0449 for Pancreas" A Randomized phase 2 trial of gemcitabine plus GDC-0449, a Hh pathway inhibitor, in metastatic pancreatic cancer.

PI Salgia/Kindler. (07/09-06/13). **Laboratory Correlates** PI Catenacci. \$35,000. 0% effort.

ALLIANCE/CALGB for Clinical Trials in Oncology Foundation YIA 07/2012-06/2013. "Laboratory Correlatives Companion Study for CALGB 80101 Evaluating MET, RON, HER2, TOP2A and ERCC1 as Biomarkers for Gastroesophageal Adenocarcinoma." \$30,000, 0% effort (07/1/12 – 6/2014)

K-12. Paul Calabresi Clinical Oncology Career Development K12 Program. "The Role of RON Tyrosine Kinase in Gastroesophageal Cancer". \$125,500/yr (10/1/10 – 9/30/13, 75% effort)

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“The role of RON tyrosine kinase in relation to targeted MET inhibition in gastroesophageal cancer.”

OSI Pharmaceuticals. 04/23/2012 – 04/22/2014 (\$140,000, 5% effort)

OncoPlex Diagnostics Collaborative Funding: OncoPlex Dx Project ID: Work Orders 3,4,6 (\$24,500 each, 2012-2014, 0% effort)

UCCCC Pilot Precision Medicine Award. “Towards Personalized Treatment of Gastroesophageal Adenocarcinoma: A Pilot Trial of PANGEA” 01/01/14-12/31/14 (\$35,000, 0% effort)

Amgen Collaborative Funding: Evaluation of MET expression and gene copy number in gastroesophageal tissues. 09/09/2013 – 09/08/2015 (\$183,500, 0.5% effort)

ITM Pilot Award: Exhaustive detection of drug resistance mutations. 9/2015-9/2016 (\$35,000, 0% effort). PI Chung-I Wu/Catenacci DVT.

K23. PANGEA-IMBBP Pilot Trial (Personalized Antibodies for GastroEsophageal Adenocarcinoma Pilot Trial). 9/11/14-8/31/17 (\$156,000/yr, 75% effort).

PI Daniel Catenacci.

Genentech Collaborative Funding: Towards Personalized Therapy of Gastroesophageal Adenocarcinoma. (\$250,000 10/2014-10/2017, 10% effort)

OncoPlex Diagnostics Collaborative Funding: OncoPlex Dx Project ID: Work Order 7. (\$140,000/yr) (\$280,000 1/14/15-1/13/18, 0% effort)

Endoscopic Research Award 2018 (PI Chapman) “Liquid Biopsies of the Portal Vein Using Endoscopic Ultrasound for Next Generation Sequencing of circulating tumor DNA for Therapeutic and Prognostic Stratification in Pancreatic Cancer.” (2018-2019) (\$60,000, 0% effort).

Ullman Scholar Award: “Evaluation of intratumoral tumor and immune cell heterogeneity” (7/2018-6-/2019 \$50,000, 0% effort).

R01 5R01CA132897-07: Bayesian Inference for Tumor Heterogeneity with Next Generation Sequencing Data from PANGEA. PI Yuan Ji (Biostatistician Northshore/University of Chicago. (2015-2020) (Catenacci 10% effort)

ORAL PRESENTATIONS

Invited Speaking

International Meetings/Conferences

May 25, 2008. “RON receptor tyrosine kinase: A novel therapeutic target of gastroesophageal adenocarcinoma.” Chinese National Genome Center, Shanghai, China.

May 26, 2008. “RON receptor tyrosine kinase: A novel therapeutic target of gastroesophageal adenocarcinoma.” First Peoples’ Hospital, Shanghai, China.

July 12, 2013 “Towards personalized treatment for gastroesophageal adenocarcinoma: strategies to address inter- and intra- patient tumor heterogeneity: PANGEA”. WIN (Worldwide Innovative Networking in Personalized Cancer Medicine) 2013 5th Annual Conference. Paris, France. **Plenary Session ORAL Presentation & Best Abstract Award.**

<http://ecancer.org/conference/328-win-symposium-2013/video/2151/strategies-to-address-inter--and-intra--patient-tumour-heterogeneity--pangea.php>

<http://www.winsymposium.org/abstracts/abstract-publication-2/>

<http://www.winsymposium.org/program/program-at-a-glance/presentations-july-12/>

January 15, 2015 “Tumor Board: Management of Challenging Cases of Upper Gastrointestinal Cancers (ARS)” Invited Panelist. ASCO GI 2015, San Francisco, CA.

June 1, 2015 “Meeting Highlights: Gastrointestinal Cancer.” ASCO Trainee & Early-Career Oncologist Lounge. ASCO 2015, Chicago IL.

January 21, 2016 GI ASCO Oral Abstract Session – Discussant. ASCO GI 2016, San Francisco, CA.

January 21, 2016 “General Session 3: Multimodal Approaches for Advanced GE Junction Cancers (East and West)–Challenging Cases” Session Chair. ASCO GI 2016, San Francisco, CA.

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June 29, 2017 GI ESMO Oral Abstract Session - Session VI Gastric Cancer LBA-009: **Catenacci DVT**, Wainberg Z, Fuchs CS, Garrido M, Bang YJ, Muro K, Savage M, Wang J, Koshiji M, Dalal RP, Kang YK. KEYNOTE-059 cohort 3: safety and efficacy of pembrolizumab (pembro) monotherapy for first-line treatment of patients (pts) with PD-L1-positive advanced gastric/gastroesophageal (G/GEJ) cancer. ESMO World GI July 28-30, 2017. *Barcelona Spain*. Oral Presentation, presented by Catenacci. Ann Oncol (2017) 28 (suppl_3): mdx302.008.

October 18, 2017 World CDx Annual Summit – Session: Clinical Implementation and Validation- “Improving Patient Recruitment and Retention on Precision Medicine Clinical Trials”. World CDx 9th Annual Summit Boston, MA.

December 14, 2017 “Perioperative systemic chemotherapy and the practical use of triplet for borderline resectable mCRC patients”. Chang Gung Memorial Hospital, Linkou District, Taiwan.

December 16, 2017 “Annual update on the treatment for metastatic colorectal cancer and its impact on personalized therapeutic approach.” Annual Meeting of the Society of Colon and Rectal Surgeons. Taipei, Taiwan.

June 19, 2018 “Gastroesophageal tumor molecular heterogeneity, molecular evolution, and implications in the clinic” Samsung Medical Center. Seoul, Korea.

June 21, 2018 Korean Cancer Association GI Gastric Cancer Plenary Session: “Overcoming tumor heterogeneity in Gastroesophageal Adenocarcinoma: the PANGAEA trial” Korean Cancer Association Annual Meeting. Seoul, Korea.

September 27, 2018 2nd Annual AACR Conference Translational Medicine, Session: Precision Cancer Medicine: “Implementing precision strategies to address molecular heterogeneity for gastroesophageal adenocarcinoma”. Sao Paulo, Brazil.

May 9, 2019 13th International Gastric Cancer Congress, Session Novel Drugs (Non-immune therapy): “Personalized treatment: How to overcome tumor heterogeneity”. Prague, Czech Republic.

June 3, 2019 ASCO 2019 Annual Meeting, Educational Session: Debate: This House Believes FLOT Is the Standard Treatment for Fit Patients With T3N1 GEJ Adenocarcinoma. Chicago IL, USA.

September 9, 2019 “Overcoming tumor heterogeneity in Gastroesophageal Adenocarcinoma: the PANGAEA trial.” Eleventh International Workshop on Pharmacodynamics of Anticancer Agents. Monestier, France.

October 19, 2019 “The role of anti-HER2 therapy in the management of Gastro-Esophageal Adenocarcinoma: Metastatic, Adjuvant, and Neo-adjuvant Settings?” Annual McGill Symposium on Upper GI malignancies. Montreal, Canada.

January 23, 2020 GI ASCO Oral Abstract Session – Discussant. ASCO GI 2020, San Francisco, CA.

March 3, 2020 Japanese Annual Gastric Cancer Meeting - Targeted therapies for targeted populations in Gastric cancer (PANGAEA), Yokohama, Japan.

National

January 13, 2010 Visiting Professor Lecture: “RON is a novel prognostic marker and therapeutic target for gastroesophageal adenocarcinoma.” Northwestern University, Chicago, IL.

March 12-14, 2010 “Novel therapies for gastroesophageal adenocarcinoma: A personalized treatment approach.” World Congress on Gastroenterology & Urology. Marriott Omaha, USA.

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June 21, 2011. "RON tyrosine kinase in cancer: no longer MET's Little Brother!" OSI/Astellas Pharmaceuticals. Farmingdale, Long Island, NY.

June 24, 2011. "RON tyrosine kinase in cancer: no longer MET's Little Brother!" AVEO Pharmaceuticals, Inc. Cambridge, MA.

October 5, 2011. "Targeted Therapies A New Generation of Cancer Treatments." OptumHealth's 20th Annual National Conference. Hyatt Regency in Minneapolis, MN.

October 20, 2011 "A Patient with Gastric Cancer Treated with a MET Inhibitor." Expert Forum on MET Inhibition. Oncology Network for Excellence. NCIR/CTEP, Bethesda, MD..

October 21, 2011. "Predicting Response to MET Targeted Agents with Biomarkers: *MET* Amplification." Expert Forum on MET Inhibition. Oncology Network for Excellence. NCI/CTEP, Bethesda, MD.

February 22-25, 2012. "MET tyrosine kinase: prognostic and predictive biomarkers of the MET pathway." 12th Annual Targeted Therapies of Lung Cancer Meeting. The Fairmont Miramar Hotel, Santa Monica, CA. Sponsored by the IASLC.

September 20, 2012. "Towards personalized treatment for gastroesophageal adenocarcinoma: strategies to address inter- and intra- patient tumor heterogeneity," Genentech, San Francisco.

October 25-26, 2012. "Gastrointestinal Cancer Overview: Gastroesophageal Adenocarcinoma, Colorectal Adenocarcinoma, Hepatocellular Carcinoma. FOCUS on MET Tyrosine Kinase." 2nd Annual Expert Forum on MET Inhibition. Oncology Network for Excellence. CTEP/NCI. Washington, DC.

October 25-26, 2012. "Gastroesophageal Adenocarcinoma: Strategies to address inter- & intra-patient tumor heterogeneity...a focus on MET." 2nd Annual Expert Forum on MET Inhibition. Oncology Network for Excellence. CTEP/NCI. Washington, DC.

October 25-26, 2012. "Colorectal Cancer: FOCUS on MET Tyrosine Kinase." 2nd Annual Expert Forum on MET Inhibition. Oncology Network for Excellence. CTEP/NCI. Washington, DC.

December 6, 2012. "Towards personalized treatment for gastroesophageal adenocarcinoma: strategies to address inter- and intra- patient tumor heterogeneity...PANGEA." AVEO Pharmaceuticals, Inc. Cambridge, MA.

April 5, 2013. "Moderated Roundtable Discussion: Defining the major knowledge gaps and priorities for future research of cholangiocarcinoma". Invited Panelist. CanLiv 3rd Annual Symposium: Harnessing Genomic-Driven Therapies for Hepatobiliary Cancers. Washington, DC.

May 18, 2013. "Treatment of Advanced Gastroesophageal Cancer: A Focus on Targeted Therapies" JACOB phase III Clinical Trial Investigators' Meeting: A double-blind, placebo-controlled, randomized, multicenter Phase III Study evaluating the efficacy and safety of pertuzumab in combination with trastuzumab and chemotherapy in patients with HER2-positive metastatic gastroesophageal junction and gastric cancer. International Investigator Meeting. InterContinental, Chicago, IL.

June 20-22, 2013. "Gastroesophageal Adenocarcinoma in The Era of Targeted Therapies: A Focus on MET" Amgen Oncology Global Advisory Board. Thousand Oaks, CA.

May 4-6, 2014. Detection of Portal Vein (PV) Circulating Tumor Cells (CTCs) in Pancreatic Cancer (PC) patients obtained by EUS guided PV Sampling. A safety and Feasibility trial. Accepted as an **Oral Presentation**. Digestive Disease Week 2014. Chicago, IL.

November 24, 2014 Visiting Professor Lecture: "Strategies to address inter- and intra- patient tumor molecular heterogeneity using next-generation companion diagnostics and PANGEA: a novel clinical trial design". Nantworks/NantHealth, Los Angeles, CA.

March 3, 2015. Visiting Professor Lecture: "Strategies to address inter- and intra- patient tumor molecular heterogeneity using next-generation companion diagnostics and PANGEA: a novel clinical trial design". Grand Rounds University of California San Diego UCSD, CA.

March 5, 2015. Visiting Professor Lecture: "Strategies to address inter- and intra- patient tumor molecular heterogeneity using next-generation companion diagnostics and PANGEA: a novel clinical trial design". Section of Oncology Weekly Meeting, Stanford University. Palo Alto, CA.

March 30/31, 2015. "Next-Generation Clinical Trials Incorporating Next-Generation Companion Diagnostics". OMICS 2nd Annual Meeting, Patrick Soon-Shiong NantOmics. Los Angeles, CA.

July 16, 2015. "Next-Generation Clinical Trials Incorporating Next-Generation Companion Diagnostics". FDA gastric cancer mini-symposium. Silver Spring, MD.

November 7, 2015 Debbie's Dream Foundation for Stomach Cancer Inaugural Chicago Symposium. Committee Chair and Organizer, Moderator, Speaker ("Tumor Genomics, Immunotherapy, Clinical Trials, and Other Hopes for the Future"), O'Hare Marriot, Chicago IL.

November 14, 2015. "Tumors to the Liver: Metastatic Adenocarcinoma of Unknown Origin – Work up before Therapy and Role of Molecular Profiling to Sort it out" Hepatic Tumor Summit, Tampa FL.

November 14, 2015. "Does Molecular Profiling Predict Response to Therapy?" Hepatic Tumor Summit, Tampa FL.

June 17, 2016. Visiting Professor Lecture: "Tumor molecular heterogeneity, molecular evolution, and implications in the clinic." Roswell Park Grand Rounds, Buffalo NY.

October 1, 2016. "Tumor Genome Analysis Includes Germline Genome!! Are We Ready For Surprises??" National Society of Genetic Counsellors 35th Annual Meeting. Seattle WA.

October 26, 2016. Visiting Professor Lecture: "Determining the Clinical Utility of Plasma ctDNA Next-Generation Sequencing". Guardant Health. Redwood City, CA.

May 12, 2017. "Addressing Tumor Molecular Heterogeneity using A Novel Clinical Trial Design – PANGEA". Symposium on Dose Selection for Cancer Treatment Drugs: Novel Clinical Trial Designs for Cancer Treatments. Stanford, Palo Alto, California.

November 3, 2017. "KEYNOTE-059: Trial Efficacy and Safety of Pembrolizumab Alone or in Combination With Chemotherapy in Advanced Gastric or Gastroesophageal Cancer." KEYNOTE-585 National Initiation Investigator Meeting, Hilton Dallas Lincoln Centre, Dallas, Tx.

January 16, 2018. Visiting Professor Lecture: "Intra-patient molecular heterogeneity a barrier to successful implementation of precision medicine in gastroesophageal adenocarcinoma – how to address?." GI Oncology Grand Rounds University of California, San Francisco University of California San Francisco UCSF. San Francisco, CA.

February 13, 2018. Visiting Professor Lecture: "Tumor molecular heterogeneity, molecular evolution, and implications in the clinic." Cancer Center Seminar, University of Texas Southwestern, Dallas, TX.

April 21, 2018. "Chemotherapy, Targeted Treatments, and Immunotherapy for Gastric and Esophageal Cancer: Hope for the Future". Debbie's Dream Foundation for Stomach Cancer 8th Annual Symposium and Live Webcast. Hollywood, FL.

August 4, 2018. "Best of ASCO 2018 : Gastrointestinal (Non Colorectal) Cancer". Best of ASCO 2018, Denver, CO.

August 6, 2018. Visiting Professor Lecture: "Tumor molecular heterogeneity, molecular evolution, and

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implications in the clinic.” Cancer Center Seminar. Yale University Medical Center. New Haven, CT.

November 2, 2018. “Gastroesophageal Adenocarcinoma Overview of Epidemiology, Molecular Profiling and Treatment.” Phase III FIGHT study Investigator Meeting: A Study of Bemarituzumab (FPA144) Combined With Modified FOLFOX6 (mFOLFOX6) in Gastric/Gastroesophageal Junction Cancer (FIGHT). The Westin Austin Downtown. Austin, Tx.

January 12, 2019. “Tumor molecular heterogeneity, molecular evolution, and implications in the clinic – testing a treatment algorithm.” Cancer Center Showcase – Precision Oncology Applications and Utility at Cancer Centers Session. The Precision Medicine World Conference (PMWC) 2019. Santa Clara, CA.

April 17, 2019. “Next-Generation Precision Oncology Trials”. The 3rd Annual Stat4Onc Conference. Hartford, CT.

June 29, 2018. “Best of ASCO 2019: Gastrointestinal (Colorectal) Cancer”. Best of ASCO 2019, St. Louis MO.

July 17, 2019. Visiting Professor Lecture: “Assessing and Addressing Tumor Genomic Heterogeneity: Plasma ctDNA Next-Generation Sequencing.” Roswell Park Cancer Center, Buffalo, NY.

August 26, 2019. “Assessing and Addressing Tumor Genomic Heterogeneity: Plasma ctDNA Next-Generation Sequencing.” Moffitt, Tampa, FL.

October 10, 2019. “Novel Targets and Immunotherapy Advances in Esophagogastric Adenocarcinoma How do we Sequence New Immunotherapy Agents?” International Society of Gastrointestinal Oncology (ISGIO) Annual Meeting. Arlington, VA.

November 4, 2019. “Gastric Cancer: Molecular subtypes and targeted therapy potential.” Collaborative Group of the Americas on Inherited Gastrointestinal Cancer (CGA-IGC) Annual Meeting. Salt Lake City, UT.

March 7, 2020. “Perioperative Chemotherapy With or Without Radiation in Patients with Early Stage Gastro-Esophageal Cancers.” Panel. Mayo Clinic Gastrointestinal Cancers 2020. San Diego, CA.

March 7, 2020. “Metastatic Refractory GE Cancer: Where Should Immunotherapy Fit into the Treatment Algorithm?” Mayo Clinic Gastrointestinal Cancers 2020. San Diego, CA.

February 18, 2021 “Advances in the management of Gastroesophageal Adenocarcinoma.” UChicago Medicine virtual CME on the Management of Metastatic Gastric Cancer

February 26, 2021. “Utilization of Molecular Analysis in Oncology Practice.” Henry Ford Health System Grand Rounds. Detroit, MI.

Regional

March 13, 2009 “Targeting Hedgehog Signaling in Cancer,” The University of Chicago Phase II Consortium 14th Annual Symposium, Gleacher Center, Chicago, IL.

March 13, 2010. “Targeting Hedgehog Signaling in Cancer,” The University of Chicago Phase II Consortium 15th Annual Symposium, Gleacher Center, Chicago, IL.

May 6, 2011. “Perioperative Therapy for Gastroesophageal Adenocarcinoma”. The 3rd Annual Controversies in the Management of Complex GI Patients Symposium. The Ritz Carlton Hotel, Chicago, IL.

September 16, 2011. “A Laboratory Correlative Companion Study for CALGG 80101 evaluating MET, RON, HER2, TOP2A, and ERCC1 as Biomarkers for Gastroesophageal Adenocarcinoma” ACTION (Alliance for Clinical Trials In Oncology Group). Hyatt Regency O’Hare, Rosemont, IL.

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Sept 15-18, 2011. "Developmental Therapeutics in Oncology: Updates from ASCO 2011 Best of ASCO Meeting". The 14th Annual APAO Conference. APAO's Best of ASCO Oncology Meeting. The Chicago Wyndham Hotel.

April 27, 2012. "Pancreatic Cancer: Hedgehog Signaling & the new era of FOLFIRINOX". The University of Chicago Phase II Consortium 17th Annual Symposium, Gleacher Center, Chicago.

April 27, 2012. "Towards Personalized Cancer Care for Gastroesophageal Adenocarcinoma: Challenge, Controversy & Consensus," The University of Chicago Phase II Consortium 17th Annual Symposium, Gleacher Center, Chicago.

September 07, 2012. "Systemic Therapy for Hepatocellular Carcinoma (HCC) and Biliary Tract Cancers," The 4th Annual Gastrointestinal Cancer Symposium: Update on the Management of GI Cancer Patients. The Ritz Carlton Hotel, Chicago, IL.

April 12, 2013. "Towards personalized treatment for gastroesophageal adenocarcinoma: strategies to address inter- and intra- patient tumor heterogeneity...PANGAEA," The University of Chicago Phase II Consortium 18th Annual Symposium, Gleacher Center, Chicago.

October 10, 2014 "Personalized Colon Cancer Care: Are we there yet?" University of Chicago Symposium: "Colon, Rectum and Beyond: Innovations in Management of Inflammatory Bowel Disease, Colorectal Cancer and Pelvic Floor Disorders". The Board of Regents Room, American College of Surgeons, North St. Clair, Chicago, IL.

January 23, 2015 "Strategies to address inter- and intra- patient tumor molecular heterogeneity using next-generation companion diagnostics and PANGAEA: a novel clinical trial design". Grand Rounds Northshore Hospital, Chicago, IL.

April 13, 2015 "Strategies to address inter- and intra- patient tumor molecular heterogeneity using next-generation companion diagnostics and PANGAEA: a novel clinical trial design". NorthShore Scientific Society meeting, Chicago, IL.

November 5, 2015 "Analyzing Your Genome". Rolfe Foundation Symposium on Personalized Medicine. Cancer Wellness Center, Northbrook, IL.

April 8, 2016. "Tumor Molecular Heterogeneity, Molecular Evolution, and Implications in the clinic" The University of Chicago Phase II Consortium 21th Annual Symposium, Gleacher Center, Chicago.

November 7, 2017. "Personalized Medicine in the Gastrointestinal Oncology Clinic: Promises, Challenges, and Future Decisions". NorthShore Gut Club Quarterly Meeting. Skokie, IL.

April 20, 2018. Translational Research in Upper GI Cancers: Gastroesophageal Cancer & Cholangiocarcinoma." The University of Chicago Phase II Consortium 23rd Annual Symposium, Gleacher Center, Chicago.

Intramural

November, 2006 "Anticoagulants, Hemostasis, and Cancer – is the link c-MET? Case Presentation and Review of the literature." University of Chicago Hematology/Oncology Section Conference.

June 25, 2007 "Cancer Stem Cells". University of Chicago Hematology/Oncology Section Conference..

Oct 27, 2008 "RON Tyrosine Kinase: A Novel Molecular Target for the Treatment of Gastroesophageal Cancer." University of Chicago Hematology/Oncology Section Conference.

Sept 14, 2009 "The Role of RON Receptor Tyrosine Kinase in Gastroesophageal Cancers – Why MET is Not Enough" University of Chicago Hematology/Oncology Section Conference.

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Chicago, IL, April 19, 2011. “Adjuvant Chemotherapy for Colon Cancer: Towards a Personalized Approach”. University of Chicago Department of Surgery Colorectal Cancer Conference.

August 3, 2011. “Career Development Seminar for Summer Research Students”. University of Chicago Laboratories.

August 29, 2011 “RON tyrosine kinase in cancer: no longer MET’s Little Brother!” University of Chicago Hematology/Oncology Section Conference.

October 10, 2011. “Novel Molecularly Targeted Therapies in Esophageal Cancer: Relevance of MET&RON” Lederer Foundation Annual Meeting. University of Chicago, Chicago, IL.

October 26, 2011. “Current trends in Colon Cancer Therapy: agents and approach” CANCER BIOLOGY 1: HUMAN CANCER PRESENTATION AND MODELING,

October 31, 2012 “Current trends in Colon Cancer Therapy: agents and approach” CANCER BIOLOGY 1: HUMAN CANCER PRESENTATION AND MODELING,.

November 27, 2012. “Adjuvant Chemotherapy for Colon Cancer: Towards a Personalized Approach”. University of Chicago Department of Surgery Colorectal Cancer Conference. Chicago, IL,

November 14, 2012 “RON upregulation is a resistance mechanism to MET directed therapy in MET driven models.” University of Chicago Department of Medicine Section of Hematology/Oncology Research Seminar, Chicago, IL.

September 25, 2013. “MET Tyrosine Kinase and GI Cancers.” University of Chicago Department of Medicine Section of Hematology/Oncology AbbVie Meeting KCBD, Chicago, IL,

February 14, 2014. “Strategies to address inter- and intra- patient tumor molecular heterogeneity using next-generation companion diagnostics and PANGAEA: a novel clinical trial design”. UCCCC Translational Seminars.

February 12, 2016. “Tumor molecular heterogeneity, molecular evolution, and implications in the clinic”. UCCCC Translational Seminars.

June 14, 2016: “Treatment of Locally Advanced and Advanced Esophagogastric Cancer”. Thoracic Surgery Fellows Conference, Chicago, IL.

March 6, 2017. Genomic Heterogeneity as a Barrier to Precision Medicine for Gastroesophageal Adenocarcinoma: An update on PANGAEA. Hematology/Oncology Section Monday Conference.

April 19, 2019. “Assessing and Addressing Tumor Genomic Heterogeneity: Plasma ctDNA Next-Generation Sequencing.” UCCCC Translational Seminars.

June 24, 2019. “Targeted Therapies for Gastroesophageal Adenocarcnioma.” Third annual UChicago-AbbVie Oncology Symposium. University of Chicago, Chicago, IL.

July 22, 2019. “Perioperative therapy for Gastroesophageal Adenocarcinoma.” Surgical Oncology Fellow Conference. University of Chicago, Chicago, IL.

INVITED, ELECTED SERVICE:

2010-2015	University of Chicago Clinical Trials Research Committee (CTRC) member
2011-	Agency for Healthcare Research and Quality (AHRQ) case reviewer, US Department of Health and Human Services.
2012-13, 2014-17	Esophago-Gastric NCI Task Force, ALLIANCE Junior Member
2013-2015	RILOMET-1 Amgen Phase III Trial Steering Committee Member
2014-2016	University of Chicago BSD Institutional Review Board (IRB) member

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2014- Data Safety Monitoring Committee: EMD Serono anti-PDL1 phase I trial.
2014- Cholangiocarcinoma Foundation Medical Advisory Committee Member
2015- Debbie's Dream Foundation for Stomach Cancer Medical Advisory Committee Member
2015- Physician Lead for the University of Chicago Cancer Center Genomic Project
2015 DOD Peer Review: Ad Hoc Reviewer Stomach Cancer
2015-2017 Hematology/Oncology Monthly Molecular Pathology Tumor Board Co-Chair
2016- Biospecimens Committee Member
2017- ASCO Esophageal Cancer Guideline Expert Panel Member
2018- AACR Gastrointestinal Cancer Research Grants Scientific Review Committee – Gastric
2018- DoD FY18 Peer Reviewed Cancer Research Program (PRCRP) – Gastric
2018-2020 ASCO SEP 7th edition Co-author (with B. Polite) for GI Chapter
2020- SWOG Vice Chair the GI Translational Medicine Subcommittee
2020- Society of Thoracic Surgeons STS & ASTRO Clinical Practice Guidelines on Multimodality Treatment of Esophageal Cancer Expert Panel Member

Editorial Activities

Ad hoc Reviewer:

<i>Journal of Clinical Oncology JCO</i>	<i>Pharmacogenomics Journal</i>	<i>Tumor Biology</i>
<i>JCO Precision Oncology JCO PO</i>	<i>Mayo Clinic Proceedings</i>	<i>JNCCN</i>
<i>New England Journal of Medicine</i>	<i>Clinical Practice</i>	<i>Lancet Oncology</i>
<i>Nature Reviews Disease Primers</i>	<i>Current Cancer Drug Target</i>	<i>Future Medicine</i>
<i>Expert Review of Anticancer Therapy</i>	<i>Clinical Investigation</i>	<i>Future Oncology</i>
<i>Journal of National Cancer Institute</i>	<i>Molecular Cancer Research</i>	<i>Cancer</i>
<i>Inflammation & Allergy Drug Discovery</i>	<i>Trends in Molecular Medicine</i>	<i>Cancer Discovery</i>
<i>Histology and Histopathology</i>	<i>The Oncologist</i>	<i>Colorectal Cancer</i>
<i>World Journal of Gastroenterology (WJO)</i>	<i>Targeted Oncology</i>	<i>Oncotarget</i>
<i>Clinical Cancer Research</i>	<i>Molecular Cancer Therapeutics</i>	<i>JAMA Oncol</i>
<i>Cancer Cell</i>	<i>Br J Cancer</i>	<i>Cancers</i>

Associate Editor:

1/2019-present *Journal of American Medical Association Network Open (JAMA Network Open)*; Oncology

Editorial Board Membership:

1/2015 – 4/2018 *World Journal of Clinical Oncology (WJCO)*
7/2016 – present *Journal of Clinical Oncology (JCO) Precision Oncology*
1/2017 – present *Cancer*
8/2020 – present *Cancers*

CLINICAL PROTOCOLS:

International PI

A Phase 2/3 Trial to Evaluate Margetuximab in Combination with INCMGA00012 and Chemotherapy or MGD013 and Chemotherapy in Patients with Metastatic or Locally Advanced, Treatment-naïve, HER2-Positive Gastric or Gastroesophageal Junction Cancer Open to Accrual 12/5/19

An International Phase 1/2 Study of GRT-C901/GRT-R902, a Personalized Neoantigen Immunotherapy, in Combination with Immune Checkpoint Blockade for Patients with Advanced Solid Tumors Open to Accrual 9/2018

FIGHT: A Phase 1/3 Study of FPA144 versus Placebo in Combination with Modified FOLFOX6 in Patients with Previously Untreated Advanced Gastric and Gastroesophageal Cancer. Open to Accrual 5/2018

A Phase 1b/2 Open Label, Dose Escalation Study of Margetuximab in Combination with Pembrolizumab in Patients with Relapsed/Refractory Advanced HER2+ Gastroesophageal Junction or Gastric Cancer. Open to accrual 4/2016

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A Phase II Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Fluorouracil in Subjects with Recurrent or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (KEYNOTE 059). Open to accrual August 2015; closed to accrual 4/2016

- **Oral presentation World GI ESMO, cohort 1**
- **Author cohorts 1, 2, and 3**

A Phase III, Multicenter, Randomized, Double-Blind, Placebo Controlled Study of Rilotumumab (AMG 102) with Epirubicin, Cisplatin, and Capecitabine (ECX) as First-line Therapy in Advanced MET-Positive Gastric or Gastroesophageal Junction Adenocarcinoma. (RILOMET-1) Amgen. Open to accrual January 2013, Terminated November 2014. Closed to accrual.

- **RILOMET-1 Steering Committee Member**
- **Senior Author on final analysis abstract ASCO 2015, first author manuscript .**

National PI

NCI-MATCH – MET amplified (C1 Arm) and exon 14 deletion (C2 Arm) arms (Crizotinib) Translational Correlatives Chair. Open to enrollment 5/2016.

A Phase 1 Open-Label, Dose-Finding Study Evaluating Safety and Pharmacokinetics of FPA144 in Patients with Advanced Solid Tumors. Open to accrual January, 2016. Closed.

Investigator Initiated Trials PI:

Use of Trifluridine/ Tipiracil (TAS-102) and Oxaliplatin as Induction Chemotherapy in Resectable Esophageal and Gastroesophageal Junction (GEJ) Adenocarcinoma. Pending opening

A phase I/II trial of Rucaparib in combination with Ramucirumab with or without Nivolumab in previously treated patients with advanced gastric and esophageal adenocarcinoma (RiME). Open to accrual 9/29/20

A Phase 1 dose finding study of the gFOLFOXIRITAX regimen using UGT1A1 genotype-directed Irinotecan with Fluorouracil, Leucovorin, Oxaliplatin and Taxotere in patients with untreated advanced upper gastrointestinal adenocarcinomas: The I-FLOAT Study. Open to Accrual 3/25/2020

A window of opportunity study of pembrolizumab in colon cancer. Open to Accrual 1/17/2020

A Phase IIa Study of Laparoscopic Hyperthermic Intraperitoneal Chemotherapy (HIPEC) and PD-L1 Expression in Gastric Cancer with Peritoneal Metastases Open to Accrual. 11/7/19

A Phase II Trial of Neoadjuvant Pembrolizumab for Resectable Early Stage Gastroesophageal Adenocarcinoma Open to Accrual. 10/11/19

PANGAEA -1MBBP Trial (Personalized Antibodies for GastroEsophageal Adenocarcinoma Pilot Trial) – NCT02213289. Open to accrual.

A pilot trial of perioperative mFOLFIRINOX with UGT1A1 genotyping for gastroesophageal adenocarcinoma – open to accrual 11/2014 - NCT02366819.

Understanding the Role of Genetics in Solid Tumor Malignancies. IRB 15-0443. Open to accrual 2/2016. PI: J Churpek, D Catenacci, H. Kindler. University of Chicago Medical Center.

A Multicenter Randomized Placebo-controlled Phase 2 Trial of Gemcitabine plus GDC-0449 (NSC 747691), a Hedgehog Pathway Inhibitor, in Patients with Metastatic Pancreatic Cancer (10052747). NCI/CTEP #8418. Opened to accrual Sept 1, 2009. (ARRA funded) Closed to accrual

Co-PI: H Kindler, D Catenacci, University of Chicago Medical Center.

- Laboratory and Radiological Correlatives, D Catenacci
- Interim Analysis presented as Poster Discussion at ASCO 2012
- Final Analysis to be presented as Poster Discussion at ASCO 2013
- *Manuscript published JCO 9/2015*

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2007-present: GI Tissue Banking Protocols:

- **Retrospective IRB 16146B – currently accruing**
- **Prospective Procurement IRB 16294A– currently accruing**
- **Prospective Procurement IRB XX – Internal NGS 1212 gene molecular panel**

PI: D Catenacci, University of Chicago Medical Center.

2004: Phase I/II Clinical Trial of Azacytidine and Arsenic Trioxide combination treatment of Myelodysplastic Syndromes.

PI: G Schiller, UCLA Medical Center. *Closed to accrual*

Site PI Pharma Sponsored:

A Phase 2, multicenter open-label, non-randomized study of bavituximab plus pembrolizumab in patients with advanced gastric or gastroesophageal cancer who have progressed on or after at least one prior standard therapy. Open to Accrual 1/21/20.

A Phase 2/3 Trial to Evaluate Margetuximab in Combination with INCMGA00012 and Chemotherapy or MGD013 and Chemotherapy in Patients with Metastatic or Locally Advanced, Treatment-naïve, HER2-Positive Gastric or Gastroesophageal Junction Cancer Open to Accrual 12/5/19

A Phase 2, open-label, single-arm trial of trastuzumab deruxtecan (DS-8201a) in HER2-positive, unresectable or metastatic gastric or gastro-esophageal junction (GEJ) adenocarcinoma subjects who have progressed on or after a trastuzumab-containing regimen. 10/1/19

A Phase 1 study of ZW49 in patients with locally advanced (unresectable) or metastatic HER2-expressing cancers. Open to Accrual 8/29/19

A Phase 3, Global, Multi-Center, Double-Blind, Randomized, Efficacy Study of IMAB362 Plus mFOLFOX6 Compared with Placebo Plus mFOLFOX6 as First-line Treatment of Subjects with Claudin (CLDN)18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma. *Open to Accrual 2/1/19.*

Trial Steering Committee Member.

An International Phase 1/2 Study of GRT-C901/GRT-R902, a Personalized Neoantigen Immunotherapy, in Combination with Immune Checkpoint Blockade for Patients with Advanced Solid Tumors *Open to Accrual 9/2018*

A Phase 1/2 Study of FPA144 versus Placebo in Combination with Modified FOLFOX6 in Patients with Previously Untreated Advanced Gastric and Gastroesophageal Cancer. Open to Accrual 5/2018 Closed to accrual

A Phase 1/2, Open-Label, Safety, Tolerability, and Efficacy Study of Epacadostat in Combination with Pembrolizumab and Chemotherapy in Subjects with Advanced or Metastatic Solid Tumors (ECHO-207/KEYNOTE-723). Open to accrual 11/2017 Closed to accrual

Combination with Cisplatin and 5-Fluorouracil versus Placebo in Combination with Cisplatin and 5-Fluorouracil as First-Line Treatment in Subjects with Advanced/Metastatic Esophageal Carcinoma (KEYNOTE-590). Open to accrual 10/2017 Closed to accrual

A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of AG-120 in Previously-Treated Subjects with Nonresectable or Metastatic Cholangiocarcinoma with an IDH1 Mutation Open to accrual May 2017 Closed to accrual

A Randomized, Multicenter, Double Blind, Phase III Study of Nivolumab or Placebo, in Subjects with Resected Lower Esophageal, or Gastroesophageal Junction Cancer. Open to accrual 8/2016. Closed to accrual Closed to accrual

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A Phase 1b/2 Open Label, Dose Escalation Study of Margetuximab in Combination with Pembrolizumab in Patients with Relapsed/Refractory Advanced HER2+ Gastroesophageal Junction or Gastric Cancer. Open 4/2016. Closed to accrual

A Phase II, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects with Advanced/Metastatic or Surgically Unresectable Cholangiocarcinoma Including FGFR2 Translocations who Failed Previous Therapy Closed to accrual 10/2018

A Phase 1b/2 Study of MEDI4736 in Combination with Tremelimumab, MEDI4736 Monotherapy, and Tremelimumab Monotherapy in Subjects with Metastatic or Recurrent Gastric or Gastroesophageal Junction Adenocarcinoma. Closed to accrual 5/2018

A Phase 1b Open-Label Study of PEGylated Recombinant Human Hyaluronidase (PEGPH20) Combined with Pembrolizumab in Subjects with Selected Hyaluronan-High Solid Tumors. Closed to accrual 4/2018.

A Phase 2, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of GS-5745 Combined with Nivolumab versus Nivolumab Alone in Subjects with Unresectable or Recurrent Gastric or Gastroesophageal Junction Adenocarcinoma. Closed to accrual 4/2017

Randomized, Double-Blind Phase 3 Study Evaluating TAS-102 Plus Best Supportive Care (BSC) Versus Placebo Plus BSC in Patients with Metastatic Gastric Cancer Refractory to Standard Treatments. Open to Accrual 4/2016, closed to accrual 11/30/17

A Phase 2, Open-label Evaluation of CRS-207 and Pembrolizumab in Adults with Recurrent or Metastatic Gastric, Gastroesophageal Junction, or Esophageal Adenocarcinomas. Terminated early.

A Randomized, Active-Controlled, Partially Blinded, Biomarker Select, Phase III Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Fluorouracil versus Placebo+Cisplatin+5-Fluorouracil as First-Line Treatment in Subjects with Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma (KEYNOTE 062). Open to Accrual 3/2016 Closed to Accrual 6/2017.

A021302: Impact of Early FDG-PET Directed Intervention on Preoperative Therapy for Locally Advanced Gastric Cancer: A Random Assignment Phase II Study. Open to accrual October 2015.

A Phase 1 Open-Label, Dose-Finding Study Evaluating Safety and Pharmacokinetics of FPA144 in Patients with Advanced Solid Tumors. Open to accrual January, 2016. Closed.

A Phase II Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Fluorouracil in Subjects with Recurrent or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (KEYNOTE 059). Open to accrual August 2015; closed to accrual 4/2016

ARQ197-A-U303 A Phase III, Randomized, Double-Blind Study of Tivantinib (ARQ 197) in Subjects with MET Diagnostic-High Inoperable Hepatocellular Carcinoma (HCC) Treated with One Prior Systemic Therapy. Open to accrual January 2013. Closed to accrual.

A Double-Blind, Placebo-Controlled, Randomized, Multicenter Phase III Study Evaluating the Efficacy and Safety of Pertuzumab in Combination with Trastuzumab and Chemotherapy in Patients with Her2-Positive Metastatic Gastroesophageal Junction and Gastric Cancer (JACOB study). Open to accrual July 2013. Closed to accrual.

A phase I open-label, non-randomized, dose-escalation first-in-man trial to investigate the c-Met kinase inhibitor EMD 1214063 under two different regimens in subjects with advanced solid tumors. Phase I expansion for MET amplification. Open to accrual November, 2013. Closed to accrual.

Phase Ib Multi-Cohort Study of MK-3475 in Subjects with Advanced Solid Tumors - Gastric/EGJ cohort PI for anti-PD1 inhibitor. Open to accrual November, 2013. Closed to accrual.

Phase 1, First-in-Human Study Evaluating the Safety, Tolerability, and

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Pharmacokinetics of AMG 337 in Adult Subjects with Advanced Solid Tumors. Open to accrual September 2013. Closed to accrual.

A Phase III, Multicenter, Randomized, Double-Blind, Placebo Controlled Study of Rilotumumab (AMG 102) with Epirubicin, Cisplatin, and Capecitabine (ECX) as First-line Therapy in Advanced MET-Positive Gastric or Gastroesophageal Junction Adenocarcinoma. (RILOMET-1) Amgen. Open to accrual January 2013, Terminated November 2014. Closed to accrual.

- *RILOMET-1 Steering Committee Member*
- **Senior Author on efficacy abstract ASCO 2015**

A Randomized, Phase III, Multicenter, Double-Blind, Placebo-Controlled Study Evaluating The Efficacy And Safety Of Onartuzumab (Metmab) In Combination With 5-Fluorouracil, Folinic Acid, And Oxaliplatin (MFOLFOX6) In Patients With Metastatic HER2-Negative, Met-Positive Gastroesophageal Cancer. Open to accrual July 2013. Closed to accrual.

A Pilot Study of neoadjuvant and adjuvant mFOLFIRINOX in localized, resectable pancreatic adenocarcinoma. Co-PI (Kindler). Closed to accrual.

A Phase 2b Randomized, Open-Label Trial of JX-594 (Vaccinia GM-CSF / TK-deactivated Virus) Plus Best Supportive Care Versus Best Supportive Care in Patients with Advanced Hepatocellular Carcinoma Who Have Failed Sorafenib Treatment. Jennerex. Closed to accrual.

ECOG E1208: A Phase III Randomized Trial of Chemoembolization with or without Sorafenib in Unresectable Hepatocellular Carcinoma (HCC) in Patients with and without Vascular Invasion. Closed to accrual.

CALGB 80802: Phase III randomized study of sorafenib (IND 69896, NSC 724772) plus doxorubicin versus sorafenib in patients with advanced hepatocellular carcinoma (HCC). Closed to accrual.

A Phase 1, Open-Label, Dose Escalation Study of ASG-5ME in Patients with Pancreatic or Gastric Adenocarcinoma. Seattle Genetics. Closed to accrual.

A Randomized, Phase II, Multicenter, Double-Blind, Placebo-Controlled Study Evaluating The Efficacy and Safety of Onartuzumab (MetMab) in Combination with 5-Fluorouracil, Folinic Acid, and Oxaliplatin (mFOLFOX6) in Patients with Metastatic HER2-Negative Gastro-esophageal Cancer. Genentech. Closed to Accrual.

Randomized, Double Blind, Phase II Study of FOLFOX Bevacizumab with MetMab versus Placebo as First Line Treatment for Patients with Metastatic Colorectal Cancer. Genentech/Sarah Cannon. Closed to Accrual.

SWOG S0809: A Phase II Trial of Adjuvant Capecitabine/Gemcitabine Chemotherapy Followed by Concurrent Capecitabine and Radiotherapy in Extrahepatic Cholangiocarcinoma (EHCC). SWOG. Closed to Accrual.

A Multicenter Randomized Placebo-controlled Phase 2 Trial of Gemcitabine plus GDC-0449 (NSC 747691), a Hedgehog Pathway Inhibitor, in Patients with Metastatic Pancreatic Cancer (10052747). NCI/CTEP. Opened to accrual Sept 1, 2009. NCI/CTEP NCI#8418. Closed to accrual (ARRA funded)

A Randomized, Double Blind Placebo Controlled Phase 2 Study of FOLFOX plus or minus GDC-0449 in patients with advanced gastric and gastroesophageal junction (GEJ) carcinoma. NCI/CTEP NCI#8376. Closed to accrual.

A Multicenter Random Assignment Phase II Study of Irinotecan and Alvocidib (flavopiridol) versus Irinotecan Alone for Patients with p53 wild type Gastric Adenocarcinoma NCI/CTEP NCI#8060. Closed to accrual.

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A Phase 2, Randomized, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of FOLFIRI in Combination With AMG 479 or AMG 655 Versus FOLFIRI for the Second-line Treatment of KRAS-mutant Metastatic Colorectal Carcinoma. Amgen. Closed to accrual.

TEACHING ACTIVITIES:

University of Chicago Medical Center, Chicago, Illinois. 2010-present

For the College (B.A., B.S.):

- (a) Didactic
 - 2011- Annual Lecture on Career Development Seminar for Summer Research Students
- (b) Clinical
 - 2011- Preceptor weekly for undergraduate students (1 student per year).

For Graduate Programs (Masters, Ph.D.):

- (a) Didactic
 - 2011- Graduate Course CANCER BIOLOGY I CABI 30800: HUMAN CANCER PRESENTATION AND MODELING: Annually one lecture on Colon Cancer
 - Graduate Course CANCER BIOLOGY III
 - Annually one lecture on Gastroesophageal Cancer
 - 2011- Annual Lecture on Career Development Seminar for Summer Research Students

For Pritzker School of Medicine (M.D.):

- (a) Didactic
 - 2011- Career Development In Oncology presentation one lecture per inpatient rotation.
 - 2011- Annual Lecture on Career Development Seminar for Summer Research Students
 - 2014 Teaching Assistant for MEDC-30011: Epidemiology and Research Design
 - Epidemiology and Research Design MEDC-30011 Medical Student (year 1) Course: Small group session Instructor.
- (b) Clinical
 - 2010- Daily inpatient rounding 4 weeks per year. 0-2 students per rotation.
 - 2011- M1 Longitudinal Program Preceptor weekly (1-2 students).

For Graduate Medical Education (Residency and Clinical Fellowships):

- (a) Didactic
 - 2010- Discussant, Medical Oncology Fellows Journal Club, Grant Writing, Board Review.
 - 2010- Annual Lecture to First Year Fellows on "Gastroesophageal", "Cholangiocarcinoma", and "Translational Medicine Basics".
 - 2012 Discussant, Internal Medicine Residents Clinical-Pathologic Correlates Conference
 - 2015 "Meeting Highlights: Gastrointestinal Cancer." ASCO Trainee & Early-Career Oncologist Lounge. ASCO 2015, Chicago IL.
 - 2016- Annual Lectures to Surgical Residents and Fellows (General and Cardiothoracic) for Esophagogastric Cancer.
- (b) Clinical
 - 2010- Daily inpatient rounding 4 weeks per year ~2-4 residents/interns, 2 fellows per rotation.
 - 2010- Supervision of fellows, residents in outpatient GI oncology clinic weekly (0-3 fellows)

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University of Chicago Medical Center, Chicago, Illinois. 2006-2010:

- Medical Student Lecture Series
 - “Myelodysplasia”, “Mesothelioma”, “Hepatocellular Carcinoma”.

UCLA Medical Center, Westwood, California. 2004-2006:

- Distinguished Teacher Award for UCLA Interns and Medical Students.
 - Teaching clinical medicine to Interns and Medical Students.

Wayne State University Medical School, Detroit, Michigan. 2000-2003:

- Tutor for individual and group sessions:
 - Anatomy, Histology, Biochemistry, Physiology, Neuroscience.

University of Waterloo, Waterloo, Ontario, Canada 1995-1999:

- Teacher Assistant in Science laboratories at University of Waterloo:
 - Cell Biology, Histology, Microbiology, 1997-1999

Lambton Kent District School Board, Sarnia, Ontario, Canada. 1997-1999:

- Summer School Teacher Assistant
 - Mathematics, Grades 9-12.

University of Chicago Research Trainees/Mentees:

Highschool Mentorship:

2012: IMSA (Igniting and Nurturing Creative, Ethical Scientific Minds that advance the human condition

Jiwon Kwak

Nitya Pariti

2018: Ocean Malka Chicago EYES on Cancer Summer Study

Undergraduate Mentorship

2011: Ciara Zagaja – Laboratory Fellowship June-August 2011.

Graduate School Mentorship

2015/16: Sravya Tumuluru - preparation for Graduate School at University of Chicago Medicine & Biological Sciences, as a technician in my laboratory

Tumuluru S, Xu D, Xu P, Henderson L, Catenacci DVT. Targeted therapies for targeted populations: MET inhibition for *MET* amplified gastroesophageal cancer. *In Preparation*

2019- Meizi Liu- “Clinical trial design using Bayesian methods” biostatistics student in the department of Public Health Science. Master’s Dissertation Committee.

Medical Student Letters/Mentorship/Teaching

2009- : Mohamed El Dinali – clinical reference letter

John Wojcik - clinical reference letter

Obinna Orji – clinical reference letter

Longitudinal Program at Pritzker for MS1

2010-2011: Christine Anterasian

David Bluhm

2011-2012: Claire Naus

Alan Hutchison

2012-2013: Chenyu Lin

Arjun Dayal

2013-2014 Jennifer Jones (MS3)

Guarav Ajmani

Daniel Camacho

2014-2015 Chijioke “CJ” Ikente

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2015-2016 Chantai Tian

2011 University of Chicago Pritzker Summer Research Program – Cluster Group Leader

Resident Mentorship

2010: Anna Halpern – (yr 3) clinical reference letter, career development
2014: Andrew Hantel – (yr 1) translational research in GI malignancies
2017-2018 Syed Abdur-Rahman – clinical trial coordinator, internal medicine residency letter application
2019- Joseph Thomas – cholangiocarcinoma MSI-High tumors and response to immune checkpoint inhibitors.

Fellow Mentorship

2010: Manish Sharma - OSI-906 clinical LOI/protocol design and submission
2011: Ahad Sadiq - ARQ197 clinical LOI for GEC first line metastatic.
Dan Geynisman - ARQ197 clinical LOI/correlates papillary renal cancer, Cholangiocarcinoma
2012: Emilio Araujo Mino - clinical reference letter
Dan Geynisman - Upper GI Malignancies
2013: Amikar Sehdev - Upper GI Malignancies
Erica Ramsdale - Upper GI Malignancies
Vassiliki Saloura - Upper GI Malignancies
Andrea Amico - Family Risk of Upper and other GI Malignancies
2014: Andrea Amico - Family Risk of Upper and other GI Malignancies

- Amico A, Nielsen S, Geynisman D, Rambo B, Carey GB, Gulden C, Facekenthal J, Olopade O, **Catenacci D**. Challenges of applying tumor genome analysis to the germline: Examples from GI Oncology. AACR Cancer Susceptibility and Cancer Susceptibility Syndromes conference. San Diego, CA. January 29-February 1, 2014.

Hollis Walker - Upper and other GI Malignancies
Jen Veneris - Upper GI Malignancies
Steve Maron - GI database procurement/Colon cancer expression analysis mass spec
Chris Chapman - Upper GI malignancies, EUS portal venous sampling for CTCs and cfDNA

- Waxman I, Chapman C, Koons A, Konda V, Siddiqui U, Gelrud A, Xu P, **Catenacci DVT**. Detection of Portal Vein (PV) Circulating Tumor Cells (CTCs) in Pancreatic Cancer (PC) patients obtained by EUS guided PV Sampling. A safety and Feasibility trial. Accepted as an Oral Presentation. Digestive Disease Week 2014. Chicago, IL. May 4-6, 2014.

2015/16: Steve Maron -Immuno-Oncology Molecular Profiling of esophagogastric cancer
-GI database procurement/Brain metastases project

- Maron S, Luke J, Hovey R, Bao R, Gajweski T, Ji Y, Seiwert T, **Catenacci DVT**. Molecular Characterization of T-Cell-Inflamed Gastroesophageal Cancer. WIN 2016, Paris France. Best Abstract and Oral Presentation.

Hollis Walker - Upper and other GI Malignancies
Nanna Sulai - Upper and other GI Malignancies
Shuang Q Zhang - Pancreatic Cancer and other Upper and other GI Malignancies

- Zhang SQ, **Catenacci DVT**. How can next-generation diagnostics aid pancreatic adenocarcinoma treatment? *Future Oncology* Mar 2016. 26831761

2016/17: Steve Maron -Immuno-Oncology Molecular Profiling of esophagogastric cancer
-GI database procurement/Brain metastases project

- Maron S, Luke J, Hovey R, Bao R, Gajweski T, Ji Y, **Catenacci DVT**. SITC annual conference, Orlando FL Feb, 2017. Identification of T cell-inflamed gastric adenocarcinoma in TCGA
- *Pectasides E, *Stachler MD, *Dersk S, *Lui Y, *Maron S, Islam M, Alpert L, Kwak H, Kindler HL, Polite BP, Sharma MR, Allen K, O'Day E, Lomnicki S, Maranto M, Kanteti R, Fitzpatrick C, Weber C, Setia N, Xiao SY, Hart J, Nagy RJ, Kim KM, Choi MG, Min BH, Nason KS, O'Keefe L, Watanabe M, Baba H, Lanman R, Agonston T, Oh DJ, Dunford A, Thorner AR, Ducar MD, Wollison BM, Coleman HA, Ji Y, Posner M, Roggin K, Turaga K, Chang P, Hogarth K, Siddiqui U, Gelrud A, Ha G, Freeman SS, Rhoades J, Reed S, Gydush G, Rotem D, Davison J, Imamura Y, Adalasteinsson,

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Lee J, Bass AJ, **Catenacci DVT**. Genomic Heterogeneity as a Barrier to Precision Medicine in Gastroesophageal Adenocarcinoma. *Epub ahead of print Oct 4 Cancer Discovery* 2017. PMID 28978556 * co-first authors

Maron SB, Catenacci DVT. Novel Targeted Therapies for Esophagogastric Cancer. *Epub Surg Oncol Clin N Am* 2017. PMID: 28279470.

Maron SB, Catenacci DVT. Update on Gastroesophageal Adenocarcinoma Targeted Therapies. *Epub Hematol Oncol Clin North Am* 2017. PMID: 28501091

- Maron SB, Lomnicki S, Chase L, Joshi S, Nagy B, Lanman R, Lee J, Catenacci DVT. 'Genomic landscape of cell-free DNA in patients with gastroesophageal adenocarcinoma' *manuscript in preparation*.

Sope Olugbile - TCR sequencing in patients (MSI-H) receiving immunotherapies

Kevin Wood - Upper and other GI Malignancies

Smita Joshi - Merck LOI perioperative immunotherapy for gastroesophageal cancer

- Joshi SS, Maron SB, Catenacci DVT. Pembrolizumab for treatment of advanced gastric and gastroesophageal junction adenocarcinoma. Nov 2. doi: 10.2217/fo-2017-0436. [Epub ahead of print] 2017 *Future Oncology*. PMID: 29094609

2017/19: Smita Joshi – GI clinical oncology, clinical trials, translational GI research

Anu Neerukonda – GI clinical oncology

2018-20 Natalie Reizine – GI Oncology, Pharmacogenomics Program, UGT1A1 genotype directed dosing of irinotecan in GI malignancies.

- Clinical trial IIT: A Phase 1 Dose Titration Study of UGT1A1 genotype directed dosing of Irinotecan combined with 5FU, leucovorin, oxaliplatin and docetaxel in patients with advanced upper gastrointestinal adenocarcinoma

2020 Joseph Heng - Upper and other GI Malignancies

2021- Carolina Soto - Upper and other GI Malignancies

Catenacci Lab Castle Foundation Scholars and Mentorship

The Castle Foundation Award is a gift provided by the Castle Foundation with intention for the fostering and training of students in the research of gastroesophageal cancer and other gastrointestinal malignancies. The funding is to support research conducted, with my supervision and mentorship, with the participation of i) students who have completed their Undergraduate Degree with the intention of applying to various Graduate Schools in in the medical field (Medical School, Graduate School, Nursing School, Physician Assistant School) or ii) Fellows completing their Oncology Fellowship with intention to have a career in Academia. A recent gift of \$1.475million over 5 years was given to this translational/laboratory research effort.

2013-2016: Les Henderson – career development --> Senior Cytogenetic Technologist, WI

- Henderson L, Peng Xu, Rambo B, Liao WL, J, Hembrough T, **Catenacci DVT**. KRAS gene amplification defines a distinct molecular subgroup of gastroesophageal adenocarcinoma that may benefit from combined anti-RAS/RAF/MEK/ERK and PIK3/PTEN/mTOR/AKT pathway inhibition. AACR KRAS Feb 21-24, 2014. Orlando FL (Abstr 55).

2013-14: Brittany Rambo Physician Assistant (see contributions in publication list above)

2015-16: Rachel Rendak Nurse Practitioner (see contributions in publication list above)

2014-16: Emily O'Day Physician Assistant (see contributions in publication list above)

2016-18: Samantha Lomnicki Medical School (see contributions in publication list above)

2017-2019 Steve Maron Coggeshall Fellow/Castle Foundation Scholar → MSKCC 12/01/18

K12 2018 - "The impact of intra-patient tumor genomic heterogeneity on immune environment heterogeneity and immune checkpoint blockade resistance."

ASCO YIA 2018 "Intra-patient tumor immune environment heterogeneity and immune checkpoint blockade resistance."

AACR YIA 2018 "Intra-patient tumor heterogeneity and checkpoint blockade resistance."

- Maron S, Alpert L, Kwak HA, Lomnicki S, Chase L, Xu D, O'Day E, Nagy RJ, Lanman RB, Cecchi F, Hembrough T, Hart J, Xiao SY, Setia N, **Catenacci DVT**. Targeted therapies for targeted populations: anti-EGFR therapy for *EGFR* amplified gastroesophageal adenocarcinoma. *Epub*

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ahead of print Feb 15 Cancer Discovery 2018.PMID 29449271

2017-2019 Leah Chase Medical School Candidate (see contributions in publication list above)
2019-21 Natalie Reizine Fellow – Pharmacogenomics and Heme/Onc Fellowship
Development of UGT1A1 genotyping and dose finding study with irinotecan in advanced GI malignancies.
Anthony Serritella PGY7 – Predictive biomarkers of treatment outcome – FCG3R SNPs
Katherine Zhou MS-IV – Predictive biomarkers of immunotherapy outcome – PDL1 and TMB heterogeneity in tissue biopsies
Ryan Johnson – MS-I - Analysis of ctDNA NGS to evaluate molecular heterogeneity and implications on targeted therapy treatment outcomes
2020- Nicole Arndt, Stephanie Moya, Bryan Peterson
Koosha Paydary

Journal of Clinical Oncology Precision Oncology/ASCO Reviewer Mentorship Program:

2019-2020 Lorenzo Gerratana, Xuemei Ji, Andrea Napolitano, Prantesh Jain.

CATENACCI

EXHIBIT B

In re: Valsartan, Losartan, and Irbesartan Products Liability Litigation
Case No. 19-2875

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AMENDED LIST OF MATERIALS CONSIDERED

MATERIALS CONSIDERED	BATES NOS.
MDL PLEADINGS AND GENERAL DOCUMENTS	
Am. Master Medical Monitoring Complaint	N/A
Am. Master Personal Injury Complaint	N/A
Am. Master Economic Monitoring Complaint	N/A
2020.12.31 Plaintiff Disclosure of Cancer Types	N/A
2021.02.11 Letter from Lori G. Cohen to Judge Vanaskie	N/A
2021.02.11 Letter from Adam Slater Providing an Overview	N/A
EXPERT REPORTS (WITH EXHIBITS)	
2021.07.04 Report of Dr. Mahyar Etminan	N/A
2021.07.06 Report of Dr. Stephen Hecht	N/A
2021.07.06 Report of Dr. Stephen Lagana	N/A
2021.07.07 Report of Dr. David Madigan	N/A
2021.07.06 Report of Dr. Dipak Panigrahy	N/A
DEPOSITION TRANSCRIPTS (WITH EXHIBITS)	
04.08.2021 – Transcript of Raphael Nudelman deposition	N/A
08.05.2021 – Transcript of David Madigan deposition	N/A
08.13.2021 – Transcript of Stephen Lagana deposition	N/A
08.17.2021 – Transcript of Stephen Hecht deposition	N/A
08.24.2021 – Transcript of Mahyar Etminan deposition	N/A
08.25.2021 – Transcript of Mahyar Etminan deposition	N/A
REGULATORY GUIDANCES AND DOCUMENTS	
Publicly Available Documents	
2011.06.02 FDA Drug Safety Communication: No increase in risk of cancer with certain blood pressure drugs--Angiotensin Receptor Blockers (ARBs)	N/A
2018.07.05 EMA: EMA reviewing medicines containing valsartan from Zhejiang Huahai following detection of an impurity: some valsartan medicines being recalled across the EU.	N/A
2018.07.13 FDA Announces Voluntary Recall, FDA News Release	N/A
2018.07.17 Teva Issues Voluntary Recall	N/A
2018.07.18 Recalled US Valsartan Labels	N/A
2018.07.27 FDA Update, Analysis of N-nitrosodimethylamine (NDMA) Levels in Recalled Valsartan in the U.S.	
2018.08.30 FDA Statement on Ongoing Investigation into Valsartan Impurities	N/A
2018.10.11 FDA Posts Redeveloped Spectrometry	N/A

MATERIALS CONSIDERED	BATES NOS.
2018.10.16 FDA Posts Alternative Spectrometry for Detecting Impurities (“Combined Direct Injection N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) Impurity Assay by GC-MS”)	N/A
2018.11.27 Teva Announces Voluntary Recall of All Amlodipine	N/A
2019.01.25 FDA Statement on the FDA’s ongoing investigation into valsartan and ARB class impurities and the agency’s steps to address the root causes of the safety issues.	N/A
2019.03.01 FDA provides update on its ongoing investigation into ARB drug products; reports on finding of a new nitrosamine impurity in certain lots of losartan and product recall.	N/A
2019.04.04 FDA Statement – Update on Recall	N/A
2019.04.15 Laboratory analysis of valsartan products	N/A
2019.05.02 Laboratory analysis of valsartan products	N/A
2019.06.13 Valisure Citizens Petition	N/A
2020.10.02 FDA Overview of Guidance for Industry	N/A
2020.12.04 - Laboratory analysis of valsartan products - FDA	N/A
2019.11.13 - FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan) <i>available at</i> https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan Last accessed September 9, 2021	N/A
FDA, GENERAL ADVICE: This letter is to inform applicants with an approved or pending application for an angiotensin II receptor blockers (ARB) drug product (DP) <i>available at</i> https://www.fda.gov/media/122643/download Last accessed September 9, 2021	N/A
COMPANY DOCUMENTS PRODUCED	
2018.07.06 Teva Health Hazard Assessment re Valsartan	TEVA-MDL2875-00274341
2018.07.06 Teva Health Hazard Assessment re Valsartan/HCTZ	TEVA-MDL2875-00274351
2018.07.10 Health Hazard Assessment of Amlodipine Valsartan	TEVA-MDL2875-00680243
2018.07.10 Health Hazard Assessment of Amlodipine Valsartan HCTZ	TEVA-MDL2875-00680244
2018.06.29 Teva Toxicological Assessment of NDMA impurity in valsartan by Dr. Nudelman	TEVA-MDL2875-00274358

MATERIALS CONSIDERED	BATES NOS.
ZHP root cause	TEVA-MDL2875-00783229
Mylan root cause	TEVA-MDL2875-00019995
2019.07.03 Teva Risk Assessment Report for Valsartan Huahai	TEVA-MDL2875-00693424
2019.07.03 Teva Risk Assessment Report for Valsartan Mylan	TEVA-MDL2875-00693422
2019.07.18 Teva Valsartan Analytical Drug Substance & Drug Product Testing Results	TEVA-MDL-0063060
2018.11.12 Tox Assessment for NDEA in Valsartan by Dr. Nudelman	TEVA-MDL-00953115
2019.03.13 Tox Assessment for NDMA and NDEA in Sartan Drugs in Parellel	TEVA-MDL2875-00773542
CBE-30 for ANDA 091519 – Valsartan/HCTZ w/ ZHP API	TEVA-MDL2875-00001886
CBE-30 for ANDA 090642 – Valsartan w/ ZHP API	TEVA-MDL2875-00013107
sANDA Approval by FDA for ANDA 091519	TEVA-MDL2875-00133642
sANDA Approval by FDA for ANDA 090642	TEVA-MDL2875-00354034
Valsartan sales	TEVA-MDL2875-00019951
Valsartan sales	TEVA-MDL2875-00019954
2019.02.15 - Email with test results	TEVA-MDL2875-00546489
2019.01.30 - Response to FDA Request for Information (RFI) for Valsartan	TEVA-MDL2875-00546490

MATERIALS CONSIDERED	BATES NOS.
Testing result of NDMA in valsartan	TEVA- MDL2875- 00546493
Balkanpharma Oupnitsa results for NOMA content in Valsartan API, manufactured by Zhejiang Huahai Co.,Ltd	TEVA- MDL2875- 00546494
Balkanpharma Oupnitsa results for NOMA content in Valsartan API, manufactured by Zhejiang Huahai Co.,Ltd	TEVA- MDL2875- 00546495
Miscellaneous Study Report	TEVA- MDL2875- 00546496
Balkanpharma Dupnitsa results for NOMA content in Valsartan tablets and Valsartan/HCT tablets	TEVA- MDL2875- 00546511
LITERATURE	
Abdel-Hamid, N. M., Nazmy, M. H., Abdel-Ghany, M. I. & Nazmy, W. H. Cytokines as important playmakers of experimental hepatocarcinogenesis confounded by diabetes. <i>Ann Hepatol</i> 11, 118-127 (2012)	N/A
Abou-Alfa GK, Macarulla T, Javle MM, et al: Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. <i>Lancet Oncol</i> 21:796-807, 2020	N/A
Abou-Alfa GK, Sahai V, Hollebecque A, et al: Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. <i>Lancet Oncol</i> 21:671-684, 2020	N/A
Adams KF, et al, Body size and renal cell cancer incidence in a large US cohort study, <i>Am J Epidemiol.</i> 2008 Aug;168(3):268-77. Epub 2008 Jun 12	N/A
Adams, carcinogenic agents in undiluted mainstream smoke and side stream smoke of different types of cigarettes. <i>Carcinogenesis</i> , 8(5):729–731	N/A
Adamson, R.H., et al., “Chemical Carcinogenesis Studies in Nonhuman Primates,” <i>Laboratory of Chemical Pharmacology, NCI-NIH</i> (1983).	N/A
Adamson RH, Chabner BA. The Finding of N-Nitrosodimethylamine in Common Medicines. <i>Oncologist.</i> 2020 Jun;25(6):460-462. doi: 10.1634/theoncologist.2020-0142	N/A
Ahotupa, M., Bussacchini-Griot, V., Bereziat, J. C., Camus, A. M. & Bartsch, H. Rapid oxidative stress induced by N-nitrosamines. <i>Biochem Biophys Res Commun</i> 146, 1047-1054, doi:10.1016/0006-291x(87)90753-4 (1987)	N/A
Aiub, C. A. et al. N-nitrosodiethylamine genotoxicity evaluation: a cytochrome P450 induction study in rat hepatocytes. <i>Genet Mol Res</i> 10, 2340-2348, doi:10.4238/2011.October.5.4 (2011)	N/A

MATERIALS CONSIDERED	BATES NOS.
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Zhu, Y., et al, “Dietary N-nitroso compounds and risk of colorectal cancer: a case-control study in Newfoundland and Labrador and Ontario, Canada,” British J. of Nutrition (2014)	N/A
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RECORDS OF BELLWETHER PLAINTIFFS	
Bonmon, Yolanda	
Plaintiff Fact Sheet	
Plaintiff Fact Sheet, 04/28/2021	YBonmon-PFS-000001 – 748
Deposition	
Bonmon, Yolanda – 2021.04.20 – Transcript	N/A
1 – 2021.04.16 Plaintiff Fact Sheet	N/A
2 – 2021.04.16 Signed Declaration of Plaintiff Fact Sheet	N/A
3 – Photograph of Valsartan Bottle	YBonmon-PPR-000319

MATERIALS CONSIDERED	BATES NOS.
4 - 2019.06.17 Amended Complaint - Master Personal Injury Complaint	N/A
5 – 2020.07.21 Bonmon Short Form Complaint	N/A
6 – Bonmon Medical Records from Charles K. Embry, MD	YBonmon-CEmbry-000001 – 88
7 – Bonmon Pharmacy Records from Apothecare Pharmacy	YBonmon-ApothPIII-000001 – 13
8 – Bonmon Medical Records from Bluegrass Women’s Healthcare	YBonmon-BlueWHC-000001 – 55
9 – Bonmon Medical Records from Central Medical Associates	YBonmon-CMA-000035 – 89
10 – Bonmon Medical Record from UK Healthcare	YBonmon-PPR-000030
11 – Bonmon Medical Records from Central Medical Associates	YBonmon-CMA-000035 – 89
12 – Bonmon Medical Records from Central Medical Associates	YBonmon-CMA-000001 – 34
13 – Bonmon Medical Records from Hardin Memorial Hospital	YBonmon-HMH-MD-000019 – 480
14 – Bonmon Medical Records from Charles K. Embry, MD	YBonmon-CEmbry-000001 – 88
15 – 2021.04.16 Plaintiff Fact Sheet	N/A
16 – Bonmon executed authorization for New Hope Foster Agency	N/A
17 – Bonmon records from New Hope Foster Homes, Inc.	YBonmon-NHFAFC-HR-000001
18 – Bonmon Executed Tax Authorization	N/A
Medical Records	
Plaintiff Produced Records	YBonmon-PPR-000001 – 658
Apothecare Pharmacy III	YBonmon-ApothPIII-000001 – 13
Bluegrass Women’s Healthcare	YBonmon-BlueWHC-000001 – 59
Central Medical Associates PLLC	YBonmon-CMA-000001 – 267
Embry Charles, MD	YBonmon-CEmbry-000001 – 88

MATERIALS CONSIDERED	BATES NOS.
Hardin Memorial Hospital	YBonmon-HMH-000001 – 521
Laboratory Corporations of America	YBonmon-LCA-000001 – 7
Lincoln Trail Diagnostics	YBonmon-LTD-000001 – 52
Norton Cancer Institute	YBonmon-NCI-000001 – 11
Norton Healthcare	YBonmon-NortonHealthcare-000001 – 559
UK Albert B. Chandler Hospital	YBonmon-UKABCH-000001 – 162
Walgreen Company	YBonmon-WC-000001 – 9
Briones, Joe	
Plaintiff Fact Sheet	
Plaintiff Fact Sheet, 02/02/2021	JBriones-PFS-000001 – 190
Medical Records	
Plaintiff Produced Records	JBriones-PPR-000001 – 441
Citizens Medical Center	JBriones-CMCen-000001 – 407
DeTar Hospital	JBriones-DeTarH-000001 – 436
Envision Pharmacies	JBriones-EnvisionP-000001 – 2
Gastroenterology of Victoria	JBriones-GVictoria-000001 – 7
HEB Pharmacy	JBriones-HEBPharm-000001 – 2
Minocha, Gulshan MD	JBriones-GKMinocha-000001 – 217
Regional Path Assocs	JBriones-RPA-000001 – 2
University of Texas MD Anderson	JBriones-UTMDACC-RD-000001 – 39

MATERIALS CONSIDERED		BATES NOS.
University of Texas MD Anderson Cancer Center		JBriones-UTMDACC-000001 – 8520
Dufrene, Lana		
Plaintiff Fact Sheet		
Plaintiff Fact Sheet, 02/10/2021		LDufrene-PFS-000001 – 186
Medical Records		
Plaintiff Produced Records		LDufrene-PPR-000001 – 178
Cardiovascular Institute of the South		LDufrene-CIS-000001 – 183
Lady of the Sea General Hospital		LDufrene-LSGH-000001 – 77
Leonard J. Chabet Medical Center		LDufrene-LJCMC-000001 – 2271
Ochsner Family Doctor Clinic		LDufrene-OFDC-000001 – 193
Racelands Pharmacy		LDufrene-RPE-000001 – 13
Walmart Pharmacy		LDufrene-WMS-000001 – 20
Garcia, Robert		
Plaintiff Fact Sheet		
Plaintiff Fact Sheet, 03/12/2021		RGarcia-PFS-000001 – 283
Medical Records		
Plaintiff Produced Records		RGarcia-PPR-000001 – 434
Baylor St. Lukes Medical Center		RGarcia-BStLMC-000001 – 831
CVS Pharmacy		RGarcia-CVS-000001 – 25
Express Scripts Inc.		RGarcia-ES-000001 – 12
HEB Pharmacy		RGarcia-HEBPharm-000001 – 25
Kelsey Pharmacy Berthelsen		RGarcia-KelseyP-000001 – 3
Kelsey Seybold Clinic		RGarcia-KSC-000001 – 2128

MATERIALS CONSIDERED	BATES NOS.
Texas Digestive Disease Consultants	RGarcia-TexasDDC-000001 – 42
Walgreen Company	RGarcia-WC-000001 – 79
Kennedy, Paulette	
Plaintiff Fact Sheet	
Plaintiff Fact Sheet, 06/21/2021	PKennedy-PFS-000001 – 470
Medical Records	
Plaintiff Produced Records	PKennedy-PPR-000001 – 590
Baylor Scott and White Medical Center	PKennedy-BS&WMC-000001 – 438
Dallas Cardiac Associates	PKennedy-DCA-000001 – 25
Dallas Nephrology	PKennedy-DallasNephA-000001 – 125
Kroger Pharmacy	PKennedy-KrogerPharm-000001 – 9
Lajara, Rosemarie, MD	PKennedy-RLajara-000001 – 10
Medical City Dallas	PKennedy-MCDH-000001 – 453
Northstar Diagnostic Imaging	PKennedy-NStarDI-000001 – 33
Solis Mammography	PKennedy-SolisM-000001 – 34
Southern Endocrinology and Diabetes Association	PKennedy-SEndo&DA-000001 – 33
Texas Breast Specialists	PKennedy-TBS-000001 – 168
Texas Colon and Rectal Surgeons	PKennedy-TC&RSurgeons-000001 – 128

MATERIALS CONSIDERED		BATES NOS.
Texas Oncology		PKennedy-T Oncology- 000001 – 385
Walgreen Company		PKennedy-WC- 000001 – 91
Dawson, Nellie		
Plaintiff Fact Sheet		
2020.05.14 Plaintiff Fact Sheet		NDawson-PFS- 000092-000180
Medical Records		
Plaintiff-Produced Medical Records		NDawson-PPR- 000001-000179
3HC Home Health Hospice Healthcare		NDawson- 3HCHH-H-HC- 000001-000114
Jordan And Assocs Gastroenterology PA		NDawson-J&AG- 000001-000068
Riverdale Family Medicine PA		NDawson-RFM- 000001-000332
UNC Health Care System Path Dept		NDawson- UNCHCS-PD- 000001-000001
UNC HealthCare System Rad Dept		NDawson- UNCHCS-RD- 000001-000001
Kinkela, Silvano		
Plaintiff Fact Sheet		
Plaintiff Fact Sheet, 06/11/2021		SKinkela-PFS- 00001 – 641
Medical Records		
Plaintiff Produced Records		SKinkela-PPR- 00001 – 430
Aaron, Jay S., MD		SKinkela- JSAaron-00001 – 85
Advance Urology Centers of New York		SKinkela- AUCNY-00001 – 33
East Virginia ENT Specialists		SKinkela- EVEN&TS-00001 – 18
Lackawanna County Dermatology Associates		SKinkela-LVDA- 00001 – 19

MATERIALS CONSIDERED	BATES NOS.
Optum Rx	SKinkela-OptumRx-00001 – 138
Pulmonary And Critical Care Specialists	SKinkela-P&CCS-00001 – 56
Sentara Leigh Hospital	SKinkela-SentaraLH-00001 – 262
Sentara Surgery Specialists	SKinkela-SSS-00001 – 749
Urology Associates of the Poconos	SKinkela-UAP-00001 – 62
Virginia Oncology Associates	SKinkela-VOA-00001 – 93
Walgreen Company	SKinkela-WC-00001 – 24
Suits, James	
Plaintiff Fact Sheet	
Fifth Amended Plaintiff Fact Sheet, 02/03/21	JSuits-PFS-001131-1224
Medical Records	
Plaintiff-Produced Medical Records	JSuits-PPR-000001-001335
Aetna US Healthcare Legal Support Svcs	JSuits-AUSH-000001-000002
John Deere - NRS	JSuits-JohnDeere-HR-000001-000001
McCaysville Internal Medicine	JSuits-McCIM-000001-000251
Mutual of Omaha Insurance Company Claims Dept	JSuits-MOIC-000001-000003
Premier Surgical Assocs Cleveland	JSuits-PremierSAC-000001-000048
Tallent Drug Store	JSuits-TDS-000001-000036
Uhlik, Allen, MD	JSuits-AUhlik-000001-000383
Lee, Robert	
Plaintiff Fact Sheet	
2020.12.23 Plaintiff Fact Sheet	RLee-PFS-000001-000167

MATERIALS CONSIDERED	BATES NOS.
Medical Records	
Plaintiff-Produced Medical Records	RLee-PPR-000001-000958
Blue Cross Blue Shield of South Carolina	RLee-BCBSSC-000001-000092
Ctrs for Medicare and Medicaid Svcs Region 4	RLee-CMMS-R4-000001-000126
Death Certificate Proof Of Authority	RLee-DCPOA-000001-000002
Family Healthcare Clinton	RLee-FH-C-000001-000404
Greenville Health System Patient Accts	RLee-GHS-BD-000001-000027
Greenville Health System Med Recs Dept	RLee-GHS-MD-000001-001985
Greenville Memorial Hosp Rad Dept	RLee-GMH-RD-000001-000017
Greenville Memorial Hospital -Billing	RLee-GMH-BD-000001-000005
Ingles Markets, Inc.	RLee-InglesM-000001-000029
Walmart Pharmacy	RLee-WMS-000001-000027
Meeks, Ronald	
Plaintiff Fact Sheet	
2021.01.15 Plaintiff Fact Sheet	RMeeks-PFS-000001-000288
Medical Records	
Plaintiff-Produced Medical Records	RMeeks-PPR-000001-006576
Central Arkansas Veterans Healthcare System Med Recs Dept	RMeeks-CAVHS-MD-000001-000011
Central Arkansas Veterans Healthcare System Path Dept	RMeeks-CAVHS-PD-000001-000002
Death Certificate Proof Of Authority	RMeeks-DCPOA-000001-000005
East Jefferson Cardiovascular Specialists Inc Med Recs Dept	RMeeks-EJCS-MD-000001-000163
East Jefferson General Hosp Path Dept	RMeeks-EastJGH-PD-000001-000001

MATERIALS CONSIDERED	BATES NOS.
East Jefferson General Hosp Med Recs Dept	RMeeks-EJGH-000751-002405
East Jefferson General Hosp Patient Accts	RMeeks-EastJGH-BD-000001-000027
East Jefferson General Hosp Rad Dept	RMeeks-EastJGH-RD-000001-000001
East Jefferson Internal Medicine	RMeeks-EJIM-000001-000057
Med Plaza ENT Physicians	RMeeks-MPENTP-000001-000036
Nola Discount Pharmacy Pharmacy	RMeeks-NDP-000001-000027
Ochsner Med Ctr Release of Information	RMeeks-OchsnerMC-MD-000001-003194
Ochsner Med Ctr Patient Accts	RMeeks-OchsnerMC-BD-000001-000124
Ochsner Med Ctr Kenner Med Recs Dept	RMeeks-OMC-K-MD-000001-000797
Ochsner Med Ctr Kenner Patient Accts	RMeeks-OMC-K-BD-000001-000010
Ochsner Med Ctr Kenner Path Dept	RMeeks-OMC-K-PD-000001-000001
Ochsner Med Ctr Kenner Rad Dept	RMeeks-OMC-K-RD-000001-000001
Ochsner Medical Complex - NR Cert Ltr	RMeeks-OMComp-000001-000001
Smith Kenneth B MD	RMeeks-KBSmith-000001-000175
Southeast Louisiana Veterans HealthCare System Rad Dept	RMeeks-SLVHCS-RD-000001-000062

MATERIALS CONSIDERED	BATES NOS.
Southeast Louisiana Veterans Health Care System	RMeeks-SLVHCS-RD-000008-000009
Tulane Univ Hosp and Clinic Rad Dept	RMeeks-TUHC-RD-000001-000003
Tulane Univ Hosp and Clinic Med Recs Dept	RMeeks-TUHC-MD-000001-000001
Univ Med Ctr New Orleans Rad Dept	RMeeks-UMCNO-RD-000001-000002
Univ Med Ctr New Orleans Patient Accts	RMeeks-UMCNO-BD-000001-000009
Univ Med Ctr New Orleans Path Dept	RMeeks-UMCNO-PD-000001-000001
Univ Med Ctr New Orleans Med Recs Dept	RMeeks-UMCNO-MD-000001-000389
Weygandt, Robert	
Plaintiff Fact Sheet	
2020.04.07 Plaintiff Fact Sheet	RWeygandt-PFS-000267-000355
Medical Records	
Plaintiff-Produced Medical Records	RWeaygandt-PPR-001547-001817
Abrams Royal Pharmacy II Pharmacy	RWeygandt-ARPharmII-000001-000002
Advanced Imaging Center	RWeygandt-AImagingCe-000001-83
Aetna US Healthcare Legal Support Svcs	RWeygandt-AUSH-000001-000013
Baylor Regional Med Ctr at Plano Med Recs Dept	RWeygandt-BRMCP-MD-000001-000307
Baylor Regional Med Ctr at Plano Path Dept	RWeygandt-BRMCP-PD-000001-000001

MATERIALS CONSIDERED	BATES NOS.
Baylor Scott and White Health Rad Dept	RWeygandt-BSW-RD-000001-000002
Baylor Scott and White Health - NRS	RWeygandt-BSW-PD-000001-000001
Baylor Scott and White Health Med Recs Dept	RWeygandt-BSW-MD-000001-000002
Baylor Scott and White Health	RWeygandt-BSW-BD-000001-17
Baylor Surgicare at Plano Patient Accts	RWeygandt-BSPlano-BD-000001-000002
Baylor Surgicare at Plano - NR Radiology Cert	RWeygandt-BSPlano-RD-000001
Blue Cross Blue Shield of Texas Claims Dept	RWeygandt-BCBST-000001-000048
Carrell Clinic - Medical	RWeygandt-CarrellC-000001-000057
Clinical Path Labs Inc	RWeygandt-CPL-000001-000004
Colon And Rectal Assocs of Texas	RWeygandt-C&RAT-000001-000027
Death Certificate Proof Of Authority	RWeygandt-DCPOA-000001-000004
DFW Smiles	RWeygandt-DFWS-000001-000018
Endocrine Assocs of Dallas	RWeygandt-EAD-000001-000342
Express Scripts Inc Recs	RWeygandt-ES-000001-000021
Fleshman James Jr MD	RWeygandt-JFleshamnJr-000001-000219

MATERIALS CONSIDERED	BATES NOS.
Heart Hosp Baylor Plano Med Recs Dept	RWeygandt-HHBP-MD-000001-000657
Hollabaugh, Eric, MD - Medical	RWeygandt-EHollabaugh-000001-000008
Lab Corp of America Med Recs Dept	RWeygandt-LabCorpA-MD-000002-000009
Legacy Heart Ctr Med Recs Dept	RWeygandt-LHC-MD-000001-000001
Med Ctr of Plano Med Recs Dept	RWeygandt-MCPlano-MD-000001-000122
Med Ctr of Plano Rad Dept	RWeygandt-MCPlano-RD-000001-000001
Med Ctr of Plano Path Dept	RWeygandt-MCPlano-PD-000001-000002
Med Clinic of North Texas PA	RWeygandt-MCNT-000001-000093
North Central Surgical Ctr	RWeygandt-NCSC-000001-000250
North Point Lab	RWeygandt-NPL-000001-000001
Plano Dermatology Assocs	RWeygant-PDA-000001-000003
Quest Diagnostics Irving	RWeygandt-QD-Irving-000001-000002
Safeway Inc Corporate Pharmacy Dept	RWeygandt-Safeway-000001-000017
Texas Health Presbyterian Hosp Dallas Patient Accts	RWeygandt-THPHD-BD-000001-000009
Texas Health Presbyterian Hosp Dallas Path Dept	RWeygandt-THPHD-PD-000001-000001

MATERIALS CONSIDERED	BATES NOS.
Texas Health Presbyterian Hosp Dallas Rad Dept	RWeygandt-THPHD-RD-000001-000001
Texas Oncology Pharmacy Sammons	RWeygandt-TOPS-000001-000002
Texas Oncology Plano Prestonwood Med Recs Dept	RWeygandt-TO-PP-MD-000001-000391
TMI Sports Medicine and Orthopedic Surgery - NR Cert	RWeygandt-TMISMOS-000001-000001
Verity Cancer Center	RWeygandt-VCC-000001-56
VerityPET CT	RWeygandt-VPET-CT-000001-000065
Verity PET CT Rad Dept	RWeygandt-VPET-CT-RD-000001-000087
Walgreen Company	RWeygandt-WC-000001-000006
Deposition	
2021.04.13 Weygandt, Martha Transcript	
1 - Plaintiff's Fact Sheet	N/A
2 - Declaration	N/A
Composite 3 - Bankruptcy petition	N/A
3 - Motion for Setting and Request for Expedited Hearing on Motion to Use Cash Collateral	N/A
4 - Master Personal Injury Complaint	N/A
5 - First Amended Short Form Complaint	N/A
6 - Medical Records	N/A
7 - Death certificate	RWeygandt-DCPOA-000001
8 - Follow Up Examination	RWeygandt-PPR-000217-229
9 - Patient Tax / Insurance	RWeygandt-Safeway-0003-17
10 - Medical Records from Endocrine Associates of Dallas, P.A.	RWeygandt-EAD-000055-60
11 - Medical Records from W B Carrell Memorial Clinic	RWeygandt-CarrellC-000003-6

MATERIALS CONSIDERED	BATES NOS.
12 - Medical Records from Cardiology	RWeygandt-HHBP-MD-000431-433
13 - Medical Records from Endocrine Associates of Dallas, P.A.	RWeygandt-EAD-000074-78
14 - Medical Records Bates 1-16 with cover page	N/A
15 - Medical Records Bates 570-605	N/A
16 - Pharmacy Defendants' Exemplar Defendant Fact Sheet	N/A
POST-MARKETING PERIODIC SAFETY REPORTS	
ANDA 077530	
Valsartan Tablets 40 mg, 80 mg, 160 mg, 320 mg	
Teva Pharmaceuticals, 01 April 2015 – 30 June 2015	N/A
Teva Pharmaceuticals, 04 January 2016 – 03 April 2016	N/A
Teva Pharmaceuticals, 04 April 2016 – 03 July 2016	N/A
Teva Pharmaceuticals, 04 July 2016 – 03 October 2016	N/A
Teva Pharmaceuticals, 04 October 2016 – 03 January 2017	N/A
Teva Pharmaceuticals, 01 January 2017 – 31 March 2017	N/A
Teva Pharmaceuticals, 01 April 2017 – 30 June 2017	N/A
Teva Pharmaceuticals, 01 July 2017 – 30 September 2017	N/A
Teva Pharmaceuticals, 01 October 2017 – 31 December 2017	N/A
Teva Pharmaceuticals, 01 January 2018 – 31 March 2018	N/A
Teva Pharmaceuticals, 01 April 2018 – 30 June 2018	N/A
Teva Pharmaceuticals, 01 July 2018 – 30 September 2018	N/A
Teva, 01 October 2017 – 31 December 2018	N/A
ANDA 090642	
Valsartan Tablets 40 mg, 80 mg, 160 mg, 320 mg	
Watson Laboratories, 05 January 2015 – 04 April 2015	N/A
Watson Laboratories, 05 April 2015 – 04 July 2015	N/A
Watson Laboratories, 05 July 2015 – 04 October 2015	N/A
Watson Laboratories, 05 October 2015 – 04 January 2016	N/A
Watson Laboratories, 05 January 2016 – 04 April 2016	N/A
Watson Laboratories, 05 April 2016 – 04 July 2016	N/A
Watson Laboratories, 05 July 2016 – 04 October 2016	N/A
Teva Pharmaceuticals, 05 October 2016 – 04 January 2017	N/A
Teva Pharmaceuticals, 05 January 2017 – 04 April 2017	N/A
Teva Pharmaceuticals, 05 April 2017 – 04 July 2017	N/A
Teva Pharmaceuticals, 05 July 2017 – 04 October 2017	N/A
Teva, 01 January 2018 – 31 December 2018	N/A
ANDA 091235	
Amlodipine and Valsartan Tablets 5/160 mg, 10/160 mg, 5/320 mg, 10/320 mg	
Teva Pharmaceuticals, 01 June 2015 – 31 August 2015	N/A
Teva Pharmaceuticals, 01 September 2015 – 30 November 2015	N/A
Teva Pharmaceuticals, 01 December 2015 – 29 February 2016	N/A
Teva Pharmaceuticals, 01 March 2016 – 31 May 2016	N/A

MATERIALS CONSIDERED	BATES NOS.
Teva Pharmaceuticals, 01 June 2016 – 31 August 2016	N/A
Teva Pharmaceuticals, 01 September 2016 – 30 November 2016	N/A
Teva Pharmaceuticals, 01 December 2016 – 28 February 2017	N/A
Teva Pharmaceuticals, 01 March 2017 – 31 May 2017	N/A
Teva Pharmaceuticals, 01 December 2017 – 28 February 2018	N/A
Teva, 01 March 2018 – 28 February 2019	N/A
ANDA 091519	
Valsartan and Hydrochlorothiazide Tablets 80/12.5 mg, 160/12.5 mg, 160/25 mg, 320/12.5 mg, 320/25 mg	
Watson Laboratories, 21 March 2013 – 20 June 2013	N/A
Watson Laboratories, 21 June 2013 – 20 September 2013	N/A
Watson Laboratories, 21 September 2013 – 20 December 2013	N/A
Watson Laboratories, 21 December 2013 – 20 March 2014	N/A
Watson Laboratories, 21 March 2014 – 20 June 2014	N/A
Watson Laboratories, 21 June 2014 – 20 September 2014	N/A
Watson Laboratories, 21 September 2014 – 20 December 2014	N/A
Watson Laboratories, 21 December 2014 – 20 March 2015	N/A
Watson Laboratories, 21 March 2015 – 20 June 2015	N/A
Watson Laboratories, 21 June 2015 – 20 September 2015	N/A
Watson Laboratories, 21 September 2015 – 20 December 2015	N/A
Watson Laboratories, 21 December 2015 – 20 March 2016	N/A
Teva Pharmaceuticals, 21 March 2016 – 20 March 2017	N/A
Teva Pharmaceuticals, 21 March 2017 – 20 March 2018	N/A
ANDA 200435	
Amlodipine, Valsartan and Hydrochlorothiazide Tablets 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg, 10/320/25 mg	
Teva Pharmaceuticals, 01 December 2014 – 28 February 2015	N/A
Teva Pharmaceuticals, 01 March 2015 – 31 May 2015	N/A
Teva Pharmaceuticals, 01 June 2015 – 31 August 2015	N/A
Teva Pharmaceuticals, 01 September 2015 – 30 November 2015	N/A
Teva Pharmaceuticals, 01 December 2015 – 29 February 2016	N/A
Teva Pharmaceuticals, 01 September 2016 – 30 November 2016	N/A
Teva Pharmaceuticals, 01 September 2017 – 31 August 2018	N/A
MISCELLANEOUS	
All Plaintiff Diagnosis & Treatment Report	
All Plaintiff Diagnosis & Treatment Report (additional data)	
All materials cited or referenced in my expert report and attachments	N/A
This list includes items Plaintiffs' experts relied upon. By so doing, Defendants and this expert are not waiving any arguments or objections related to admissibility.	N/A

CATENACCI

EXHIBIT C

Below is my fee schedule:

- 1) \$1500 retainer (not included towards review time)
- 2) \$600/hour for review and discussion
- 3) \$750/hour for written reports, deposition preparation, deposition, trial preparation
- 4) \$7500/day for trial

CATENACCI

EXHIBIT D

PRIOR TESTIMONY OF DANIEL CATENACCI, M.D.**As of August 2, 2021****Trial**

1. *Brown v. Sekon*, Baltimore, MD. Trial testimony given 11/19/18
2. *Allen v. St. Luke's*, Idaho. Trial testimony given 4/1/19
3. *Torres v. Summers*, Circuit Court of St. Louis City, State of Missouri, Case No. 1722-CC10764. Trial testimony given 5/15/19
4. *Karen Korszenobojn-Berger v. Andrew Berger*, Sup. Ct. of New York, Kings County, Case No. 508237/2016E. Trial testimony given 7/8/19.

Deposition

1. *Wilcoxon v Gastroenterology & Nutritional Services*. Deposition given 3/16/21.
2. *Perkins v. Trinity*. Deposition given 1/11/21.
3. *Holbrook and Frohlichstein v. Washington University Clinical Assoc., et al.*, Circuit Court of the State of Missouri, Case No. 1922-CC1091, Deposition given 10/14/20
4. *Overstreet v. Fronda*. Deposition given 10/14/20
5. *Young v. Makhdoom*. Deposition given 8/4/20
6. *Creech v. Carolina Radiology Consultants, P.A. and Jeffrey E. Jones, M.D.* Deposition given 8/20/19 and 2/24/20
7. *Gross v. BNSF*. Deposition given 10/22/19
8. *Lopez v. United States*. Deposition given 8/2/19
9. *Torres v. Summers*, Circuit Court of St. Louis City, State of Missouri, Case No. 1722-CC10764. Deposition given 2/25/19.
10. *Allen v. St. Luke's, et al.* Deposition given 1/14/19
11. *Teresa Brown v. Jatinder S. Sekhon, M.D.* Deposition given 5/11/18
12. *Larry Ames v. Donne Graessle D.O.*, Circuit Court of Jackson County, Missouri, Case No. 1516-cv-18185. Deposition given 6/7/17
13. *Lerner v. Kelly*. Deposition given 2/24/17
14. *Robert Adams v. Poirot & Macoupin Family*. Deposition given 1/25/17

Exhibit C

1 UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY
2
3 IN RE: VALSARTAN, LOSARTAN,)
AND IRBESARTAN PRODUCTS)
4 LIABILITY LITIGATION)
_____) MDL No. 2875
5)
THIS DOCUMENT RELATES TO ALL)
6 CASES)
7
8

9 CONFIDENTIAL INFORMATION - SUBJECT TO PROTECTIVE ORDER
10
11

VIDEO DEPOSITION OF DANIEL CATENACCI, M.D.
12 VIA VIDEOCONFERENCE
13 September 14, 2021
9:20 a.m.

14 Volume 2

15
16
17
18 Reporter: John Arndt, CSR, CCR, RDR, CRR
19 CSR No. 084-004605
CCR No. 1186
20
21
22
23
24

<p style="text-align: right;">Page 279</p> <p>1 DEPOSITION OF DANIEL CATENACCI, M.D., 2 produced, sworn, and examined via videoconference on 3 September 14, 2021, in the City of Chicago, State of 4 Illinois, before John Arndt, a Certified Shorthand 5 Reporter and Certified Court Reporter. 6 7 APPEARANCES OF COUNSEL 8 (All present via videoconference) 9 10 On Behalf of Plaintiffs: 11 Mazie Slater Katz & Freeman, LLC 12 103 Eisenhower Parkway, 2nd Floor 13 Roseland, NJ 07068 14 (973) 228-9898 15 BY: ADAM M. SLATER 16 aslater@mazieslater.com 17 JULIA S. SLATER 18 jslater@mazieslater.com 19 CHRISTOPHER J. GEDDIS 20 Kanner & Whiteley, LLC 21 701 Camp Street 22 New Orleans, LA 70130 23 (504) 524-5777 24 BY: LAYNE HILTON lhilton@kanner-law.com 25 26 On Behalf of Teva: 27 Greenberg Traurig, LLP 28 One International Place, Suite 2000 29 Boston, MA 02110 30 (617) 310.6231 31 BY: NICHOLAS A. INSOGNA 32 insognan@gtlaw.com 33 34 Greenberg Traurig, LLP 35 4 Embarcadero Center, Suite 3000 36 San Francisco, CA 94111 37 (415) 655-1285 38 BY: KATE WITTLAKE 39 wittlakek@gtlaw.com</p>	<p style="text-align: right;">Page 281</p> <p>1 APPEARANCES OF COUNSEL (CONTINUED) 2 3 Martin, Harding & Mazzotti LLP 4 PO Box 15141 5 Albany, NY 12212 6 (518) 724-2207 7 BY: ROSEMARIE RIDDELL BOGDAN 8 rosemarie.bogdan@1800law1010.com 9 On Behalf of CVS and Rite Aid: 10 Barnes & Thornburg LLP 11 11 S. Meridian Street 12 Indianapolis, IN 46204 13 (317) 231-6491 14 BY: KARA M. KAPKE 15 kara.kapke@btlaw.com 16 On Behalf of Zhejiang Huahai Pharmaceutical Co., Ltd., 17 Princeton Pharmaceutical Inc., Huahai U.S. Inc., and 18 Solco Healthcare U.S., LLC: 19 Duane Morris LLP 20 865 South Figueroa Street, Suite 3100 21 Los Angeles, CA 90017 22 (213) 689-7424 23 BY: ROBERT KUM 24 rkum@duanemorris.com 25 For Aurobindo Pharma Ltd., Aurolife Pharma LLC, 26 and Aurobindo Pharma USA, Inc.: 27 Cipriani & Werner, P.C 28 450 Sentry Parkway, Suite 200 29 Blue Bell, PA 19422 30 (610) 862-1929 31 BY: JESSICA M. HEINZ 32 jheinz@c-wlaw.com 33 34 Also present: 35 Elena Williams (Associate Litigation Counsel at 36 Viatrix) 37 38 James Arndt (videographer)</p>
<p style="text-align: right;">Page 280</p> <p>1 APPEARANCES OF COUNSEL (CONTINUED) 2 3 Greenberg Traurig, LLP 4 3333 Piedmont Road NE, Suite 2500 5 Atlanta, GA 30305 6 (678) 553-2103 7 BY: VICTORIA DAVIS LOCKARD 8 lockardv@gtlaw.com 9 Pietragallo Gordon Alfano Bosick & Raspanti, LLP 10 One Oxford Centre 11 301 Grant Street, 38th Floor 12 Pittsburgh, PA 15219 13 (412) 263-1816 14 BY: CLEM C. TRISCHLER 15 cct@pietragallo.com 16 FRANK H. STOY 17 fhs@pietragallo.com 18 Walsh Pizzi O'Reilly Falanga LLP 19 100 Mulberry Street, 15th Floor 20 Newark, NJ 07102 21 (973) 757-1100 22 BY: LIZA M. WALSH 23 lwalsh@walsh.law 24 25 On Behalf of Sciegen Pharmaceutical and H.J. Harkins 26 d/b/a Pharma Pac: 27 Hinshaw & Culbertson LLP 28 53 State Street, 27th Floor 29 Boston, MA 02109 30 (617) 213-7045 31 BY: GEOFFREY M. COAN 32 gcoan@hinshawlaw.com 33 Morgan Law Firm, Ltd. 34 55 W. Wacker Drive, 9th Floor 35 Chicago, IL 60601 36 (312) 327-3386 37 BY: SCOTT A. MORGAN 38 Levin Papantonio Rafferty 39 316 South Baylen Street 40 Pensacola, FL 32502 41 (850) 435-7013 42 BY: DANIEL NIGH dnigh@levinlaw.com</p>	<p style="text-align: right;">Page 282</p> <p>1 INDEX OF INTERROGATION 2 Examination by Mr. Slater Page 283 3 Examination by Mr. Insogna Page 385 4 Examination by Mr. Kum Page 411 5 Examination by Mr. Slater Page 419 6 7 INDEX OF EXHIBITS 8 9 Exhibit 13 Page 283 10 (2018 Pottgard study) 11 12 Exhibit 14 Page 283 13 (2021 Gomm study) 14 Exhibit 15 Page 320 15 (2019 Hidajat article) 16 17 Exhibit 16 Page 368 18 (2020 Adamson editorial) 19 (All exhibits are attached.) 20 21 22 23 24</p>

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1 THE VIDEOGRAPHER: We are back on the
2 record for the continuation of the deposition of Daniel
3 Catenacci, M.D. Today's date is September 14th, 2021,
4 and the time is 12:09 PM Central Standard Time.
5 Counsel, please continue.
6 MR. SLATER: Thank you.
7 EXAMINATION
8 BY MR. SLATER:
9 Q. Hello, Doctor.
10 THE REPORTER: Oh, he's muted.
11 [Discussion off the record.]
12 [Exhibit 13 marked for identification.]
13 [Exhibit 14 marked for identification.]
14 BY MR. SLATER:
15 Q. Doctor, I'm going to start with some
16 questions about the Gomm study, so if you have that
17 handy, perhaps -- I assume you probably have it right
18 in front of you.
19 A. Right where we left off, yes.
20 Q. Exactly. Okay. You speak on Page 39
21 about the Gomm study, which was published in 2021;
22 right?
23 A. Yes.
24 Q. And looking at Page 357 of that article,

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1 there is a statement in the right-hand column, first
2 paragraph, right at the bottom of that paragraph that
3 says NDMA is one of the most potent mutagenetic
4 carcinogens in animal models. I'm going to stop there.
5 Do you agree with that statement?
6 A. I agree with it similarly to the other
7 paper that this was pointed out, that it's
8 carcinogenetic in high doses, yes, in models, in animal
9 models.
10 Q. Has NDMA been shown to be mutagenetic in
11 animal models where what you would term a high dose was
12 not given to the animal?
13 A. I am not following the question.
14 Q. Is there any animal study you're aware of
15 where cancer was caused to the animals by NDMA where a
16 high dose, as you would define that term, was not given
17 to the animal or a lower dose was given?
18 A. If I understand the question correctly --
19 say, for example, if we're looking at one cancer type,
20 and so you're asking -- let's focus on liver cancer.
21 Are there models that show liver cancer at
22 high doses? Yes. Like, for example, the rat model.
23 But there are other models -- say, the nonhuman
24 primates -- at high doses for NDMA that do not show

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1 liver cancer, if that's the question.
2 Or is the question, are there models at
3 low doses that show the same cancer?
4 Q. Let me ask it a little bit differently.
5 The scientific consensus in the peer-reviewed
6 literature is that NDMA is one of the most potent
7 mutagenetic carcinogens in animal models.
8 Do you agree with that statement?
9 MR. INSOGNA: Object to form.
10 A. I agree with that with the understanding
11 that that's not taking into account the dosing of it,
12 and -- which is what is at play here in the question
13 that I was asked --
14 BY MR. SLATER:
15 Q. So the peer-reviewed literature, in your
16 opinion, is deficient because, for example, in this
17 peer review article that you're relying on heavily,
18 they don't point out that it has to be at very high
19 doses, as you would term it, so all these articles are
20 in error?
21 A. These are just incomplete sentences about
22 the details of that statement. This is an introductory
23 paper saying an overview of this topic, and it's -- but
24 it's not going into the details of what that statement

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1 means.
2 Q. So incomplete sentence after incomplete
3 sentence exists across the literature in this area;
4 right?
5 That's what your testimony is?
6 MR. INSOGNA: Object to form.
7 A. No, I'm trying to answer the question with
8 the understanding that I wouldn't just give a blank
9 approval to that statement without considering what I
10 said -- the dose and the duration of that agent or any
11 agent when talking about something like that.
12 BY MR. SLATER:
13 Q. You agree that NDMA is a mutagenetic
14 carcinogen; correct?
15 A. In animal models at certain doses, it is
16 and has been shown to be, yes.
17 Q. Go to Page 360, please. On the top
18 right-hand column -- actually, the right-hand column in
19 the middle of the page -- there's a heading that says
20 regulatory and public health implications.
21 Do you see that?
22 A. Yes.
23 Q. And the authors state about halfway down
24 that paragraph, "The immediate recall of all

<p>Page 287</p> <p>1 potentially NDMA-contaminated valsartan drug products 2 by regulatory authorities worldwide was necessary in 3 order to protect the public health." 4 Do you see that? 5 A. I see that sentence, yes. 6 Q. And that sentence was made in one of the 7 two articles that you have already told us are the two 8 most important pieces of literature in the scientific 9 literature that you're relying on; right? 10 MR. INSOGNA: Object to form. 11 A. This statement is in those papers, and 12 my -- are you asking me what the interpretation of this 13 statement is? 14 BY MR. SLATER: 15 Q. No, I was asking you to confirm that that 16 statement's found in the Gomm study, which was one of 17 the two studies that you say you're relying on above 18 all else, along with Pottegard? 19 MR. INSOGNA: Object to form. 20 A. This statement is in a paper that I relied 21 on from the data to evaluate whether or not there was 22 an increased risk in cancer from trace impurities in 23 these drugs. This statement has no bearing on that 24 assessment.</p> <p>Page 288</p> <p>1 BY MR. SLATER: 2 Q. Well, when the authors say that it was 3 necessary in order to protect the public health, 4 they're saying that because of the risk that the 5 contamination with NDMA could cause cancer to humans, 6 it was necessary to stop selling those contaminated 7 pills; right? 8 MR. INSOGNA: Object to form. 9 A. My interpretation of this is to say that 10 if there was a potential risk, it was necessary to 11 evaluate whether there was or not and not continue to 12 use those medications. That doesn't prove that there 13 was an association or that these caused that. They're 14 just stating that it was necessary to make an 15 evaluation whether or not that that existed, and in 16 their paper they conclude there is no association with 17 cancer. 18 BY MR. SLATER: 19 Q. The regulatory authorities not only 20 ordered the recall to protect the public health, but 21 made a decision that pills with the levels of NDMA that 22 were seen, certainly over 96 nanograms, should not be 23 sold ever again; right? 24 MR. INSOGNA: Object to form.</p>	<p>Page 289</p> <p>1 A. I think I answered that before, but I'll 2 say that they made this recall to ensure there wasn't a 3 risk, to evaluate if there was a risk, and during that 4 time to not continue giving the medications. 5 BY MR. SLATER: 6 Q. And the conclusion was there is a risk -- 7 over 96 nanograms, you can't sell it anymore; right? 8 MR. INSOGNA: Object to form. 9 A. That's not their conclusion in this paper, 10 no. 11 BY MR. SLATER: 12 Q. No, I'm not saying Gomm. I'm talking 13 about the FDA. 14 MR. INSOGNA: Dr. Catenacci is not 15 offering regulatory opinions. 16 MR. SLATER: I'm just -- well, let me 17 ask -- all right. Here's the question. 18 BY MR. SLATER: 19 Q. The FDA determined that there was too much 20 risk to sell these pills over 96 nanograms of NDMA; 21 right? 22 That was the level they eventually set; 23 right? 24 MR. INSOGNA: Same objection.</p> <p>Page 290</p> <p>1 A. According to their statements online that 2 we talked about before, they made an assessment to take 3 these off the market and to evaluate whether or not 4 there was a risk based on some evidence, but in the 5 meantime when it was safe to do so, when there were 6 replacement medications that did not have the 7 impurities, to then go do that, but I think as we 8 mentioned before, even with such potential risks that 9 it was still deemed to be a lower risk than stopping 10 the medications themselves. 11 BY MR. SLATER: 12 Q. While getting onto a new medication over 13 the next several days or weeks; correct? 14 A. Or months, or whatever it was. Right. 15 Q. Let's go to Page 359, the very bottom, 16 please. At the very bottom of the right-hand column 17 they're talking about some limitations of the study, 18 and they say at the bottom of the page, "A further 19 limitation is that due to the limited follow-up time, 20 we were not able to monitor the long-term effects of 21 NDMA-contaminated valsartan for more than three years." 22 Correct? 23 A. Yes. 24 Q. And you would agree this is a short-term</p>
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1 study and they were not able to evaluate long-term
2 effects; right?

3 MR. INSOGNA: Object to form.

4 A. This is similar to the question about the
5 same limitation in the other study, the Pottegard
6 study, that we talked about before, and that with the
7 current data that we have and the evidence that we
8 have, they were assessing a question that can be
9 assessed, which is this is how long we've got follow-up
10 based -- since -- on the time frame that we're dealing
11 with here.

12 So their analysis, which is appropriate,
13 and their acknowledged limitation is that it's looking
14 at this much follow-up time. So that doesn't imply,
15 though, that by default it's true that longer-term it's
16 going to show that. This is always -- all they're
17 concluding here is that there's no association during
18 the follow-up time that we've done.

19 BY MR. SLATER:

20 Q. Is the answer to my question yes, I'm
21 correct?

22 MR. INSOGNA: Object to form.

23 BY MR. SLATER:

24 Q. They couldn't study long-term effects

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1 because it was a short-term study?

2 A. That is what the statement implies and
3 that's -- I would agree that's clearly the case.

4 Q. Just above what I had read on Page 359,
5 about six or eight lines above that, they state,
6 "Although detailed batch-wise information on
7 potentially NDMA-contaminated valsartan was provided,
8 we had no information on the exact NDMA content of
9 individual valsartan tablets."

10 Do you see what I just read?

11 A. Yes.

12 Q. And that lack of knowledge about the
13 actual exposure levels was a limitation, according to
14 the authors; right?

15 A. This, again, is a similar limitation
16 across the two epi studies in that we don't know that
17 precisely and that patients may be -- may or may not be
18 getting the medications, but this is what reflects the
19 reality of what was happening, that they may have been
20 getting it for one prescription and then not the
21 next -- in the drugs themselves -- we don't know the
22 exact values, that is random and intermittent and
23 certainly not going to be at the highest level the
24 whole time.

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1 And this of course is a limitation that we
2 don't know precisely what's in every pill, but we're
3 looking at patients who had suspected lots that had the
4 impurities, and they're accounting for that, so this is
5 what's reflecting the reality of the question of these
6 potential exposures.

7 Q. And the -- rephrase. And they're also
8 commenting on the reality of the quality of the data
9 they had to rely on and they're acknowledging, as you
10 have, that there are gaps in the data about whether or
11 to what extent people on both sides of the study did
12 actually consume contaminated pills; correct?

13 MR. INSOGNA: Object to form.

14 A. Yeah, I think that when they talk about
15 the limitations they appropriately in a study such as
16 this indicate that, despite doing as many adjustments
17 and considering as many factors, that there may still
18 be residual confounding.

19 BY MR. SLATER:

20 Q. There's no randomization in this study, or
21 in Pottegard for that matter; right?

22 A. No, there is not.

23 Q. And that's an issue with any study of an
24 insurance database; correct? You just -- people are

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1 self-selected before the study is actually done, so you
2 can't randomize; correct?

3 A. That's a limitation of any study that's
4 not a randomized study, whether it be a cohort study or
5 case control, or --

6 Q. Looking now at Page 359 in the top left.
7 The Gomm authors actually comment on the Pottegard
8 study; correct?

9 A. They do.

10 Q. One thing that is stated is that the
11 Danish registry study by Pottegard, et al, has only a
12 small sample size comprising 5,150 persons with
13 prescription of valsartan.

14 And you would agree that that's a weakness
15 of the Pottegard study, that small number of people;
16 right?

17 A. That is a relative weakness compared to
18 Gomm, that it's smaller.

19 Q. Going down a little bit further in that
20 paragraph, the authors state, "However, the number of
21 cancer cases in the Danish study was limited, 302
22 cancers overall, only eight cases each of kidney and
23 bladder cancer. The statistical power for detection of
24 small effects is therefore limited and no precise

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<p>1 statements on small effect sizes can be made." 2 You would agree with that statement as 3 well; correct? 4 A. I do. 5 Q. And if we flip back to Page 357, please. 6 In the right-hand column, the second paragraph, about 7 six or seven lines down, there's a sentence that says, 8 "However, the sample size of the Danish study was 9 limited to a total of 5,150 patients, which may explain 10 the nonsignificance of the results." 11 You would agree with that statement as 12 well; correct? 13 MR. INSOGNA: Object to form. 14 A. That is a hypothesis to explain why the 15 study was negative. 16 BY MR. SLATER: 17 Q. It's a reasonable hypothesis; right? 18 A. It's a hypothesis that could be tested. 19 Q. In this study, do you have an 20 understanding as to how they established whether or not 21 someone took contaminated valsartan or not? 22 A. In the Gomm study? 23 Q. Correct. 24 A. Let me look to the methods here to ensure.</p>	<p>1 patients were filling prescriptions during that period, 2 et cetera. 3 So it's all very clearly laid out here how 4 they looked at the data, how they determined who was 5 and who wasn't, when they were, and to look at this as 6 best as possible with the limitations that we mentioned 7 that some of the information just wasn't available. 8 They looked at as many of the parameters as possible to 9 limit the bias as much as possible. 10 Q. Coming back to my question, I'm really 11 just trying to focus on how they determined whether or 12 not pills were contaminated or not, and looking at 13 where you are reading from on -- or what you're looking 14 at on Roman Numeral 2 page -- there's a sentence that 15 says the marketing authorization holders -- let me 16 start over. 17 Coming back to my question about how the 18 authors determined whether pills were contaminated or 19 not, they state here on Roman Numeral 2 under exposure, 20 "The marketing authorization holders provided 21 batch-related data on all valsartan drug products for 22 the years 2012 to 2017. This included detailed 23 information on which batches were manufactured using 24 the active ingredient valsartan supplied by ZHP and how</p>
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<p>1 Under the electronic methods, under exposure. 2 Q. So you're on the page with the little 3 Roman Numeral 2 in the bottom left? 4 A. Yes, we can start there. So the details 5 here are telling us how they accounted for -- first of 6 all, they had -- all patients included in the study had 7 a prescription for valsartan, and then they explain how 8 they determined who was exposed to potential impurity 9 and who wasn't. 10 They talk about how they determine the 11 levels when they look at -- within the exposed gift, 12 how many were getting higher doses based on the 13 pharmaceutical registration numbers of any product that 14 had recall for valsartan during that time period. 15 And they then looked at the amount of the 16 potential or possibly contaminated versus probably 17 contaminated by these records to be able to stratify 18 within those that were exposed and to the dose levels, 19 to look at that, whether or not there was a dose 20 response relationship. 21 They took into account another -- a number 22 of other factors like long-term users versus those that 23 weren't, and the definition of that is in here based on 24 how many of the quarters during the study period the</p>	<p>1 many packages of these drug products were sold. Based 2 on this information, we calculated the proportion of 3 all packages of valsartan drug products sold made up by 4 packages manufactured using contaminated ingredients." 5 Do you see what I just read? 6 A. Yes. 7 Q. So tell me if I'm right. Similar to 8 Pottegard, the Gomm authors established contamination 9 based on whether the API was manufactured by ZHP and 10 that's how they established contamination; correct? 11 MR. INSOGNA: Object to form. 12 A. I think in this one what is a little 13 different, you -- taking on right from that sentence 14 you left off on, it says, "We calculated this ratio for 15 all pharmaceutical registration numbers affected by the 16 recall of valsartan drug products." That's the exact 17 next sentence right after you stopped. 18 And the other thing I read into it in the 19 actual methods section where they're talking more 20 superficially about what they did, but they said, 21 example, ZHP products. So in other words, it's not 22 limited to ZHP products, but it's any recalled 23 valsartan drug product, according to how this reads. 24 And so as opposed to the Pottegard study</p>

<p style="text-align: right;">Page 299</p> <p>1 where I think we had already discussed and you 2 mentioned we talked about how there were the three 3 groups, whether they were exposed to ZHP or not, this 4 one, which was conducted later and published later 5 where it was done after the fact where more of the 6 recalled products were known at the time, they, 7 according to this statement, used any pharmaceutical 8 registration number affected by the recalls of 9 valsartan drug products.</p> <p>10 So I read into that because they had more 11 information, they accounted for all of those -- all of 12 the products that were known at the time that had been 13 recalled.</p> <p>14 BY MR. SLATER:</p> <p>15 Q. Actually, what they do is what I just 16 read. They say they based it on did the pill come with 17 ZHP API, and then in another place they say, for 18 example, ZHP.</p> <p>19 They say basically two different things; 20 right?</p> <p>21 MR. INSOGNA: Object to form.</p> <p>22 A. They say, example, in the area I mentioned 23 to -- and where you read you say that this is one of -- 24 this is what they're using, is ZHP, but then the</p>	<p style="text-align: right;">Page 301</p> <p>1 right?</p> <p>2 A. I read it as being that they are using 3 anything at the time of this study that had been 4 recalled.</p> <p>5 Q. If they limited it to -- well, rephrase. 6 I'll withdraw that.</p> <p>7 There's a risk of residual confounding in 8 this study; correct?</p> <p>9 A. I think that we mentioned that earlier, 10 yes. There's always risk of residual confounding in 11 studies like this, even with the best efforts to 12 account for confounding variables.</p> <p>13 Q. For example, there's no information about 14 who in the study had potential influencing factors, 15 such as smoking, nutritional habits, genetics?</p> <p>16 Those factors were not integrated into the 17 analysis; correct?</p> <p>18 A. That's right.</p> <p>19 Q. That would be a weakness of the study; 20 correct?</p> <p>21 MR. INSOGNA: Object --</p> <p>22 BY MR. SLATER.</p> <p>23 Q. It's inherent to the data, but it's a 24 weakness; correct?</p>
<p style="text-align: right;">Page 300</p> <p>1 following sentence they said any recalled valsartan 2 drug product.</p> <p>3 BY MR. SLATER:</p> <p>4 Q. And they say they calculated this ratio. 5 Do you have an understanding of what ratio 6 they're referring to?</p> <p>7 A. For all pharmaceutical registration 8 numbers affected by the recalls. So --</p> <p>9 Q. So they're looking at the -- well, you 10 answer.</p> <p>11 MR. INSOGNA: I'm sorry. What's the 12 question that's pending?</p> <p>13 BY MR. SLATER:</p> <p>14 Q. Where they refer to the -- we calculated 15 this ratio. What ratio are they talking about?</p> <p>16 A. The proportion of all packages of 17 valsartan drug products sold made up of packages 18 manufactured using contaminated ingredients. The 19 sentence just before that.</p> <p>20 Q. And we have this what I'm terming a 21 conflict where their definition of contaminated -- in 22 one place it says ZHP in another place it says, for 23 example, ZHP.</p> <p>24 It's not really clear which one it is;</p>	<p style="text-align: right;">Page 302</p> <p>1 A. It's a weakness to the data in that it 2 doesn't account for known risk factors for cancer. I 3 think that ultimately usually those types of 4 confounders would -- not accounting for them could lead 5 to false positive signals in the study.</p> <p>6 Q. Look, please, at Table 1.</p> <p>7 A. Table 1. Okay.</p> <p>8 Q. On my reading of this table, it appeared 9 that the unexposed group or the presumed unexposed 10 group was generally healthier than the, quote/unquote, 11 "exposed group." I saw less diabetes, less heart 12 failure, less polypharmacy.</p> <p>13 Would you agree with that assessment of 14 the two groups?</p> <p>15 A. I noticed the same, that most of these 16 risk factors had a higher percentage of patients that 17 were in the exposed group, yes. I would also point out 18 things like spironolactone, which is a drug that's 19 often given in the setting of cirrhosis of the liver, 20 since that I think is pertinent and relevant to this 21 particular paper that I'm sure we'll get to.</p> <p>22 And also just the bigger one at the 23 bottom, the Charleston comorbidity index, which sort of 24 summarizes all of those things, all comorbidities -- is</p>

<p style="text-align: right;">Page 303</p> <p>1 higher in the one -- the patients who have higher 2 comorbidity indexes, there's a higher percentage of 3 them in the exposed group. So that's an important 4 factor for sure, yes. 5 Q. And those factors can be strong 6 confounders that traditional statistical techniques 7 cannot always control; correct? 8 A. Potentially, yeah. And especially when 9 you try to -- that doesn't necessarily mean you've been 10 able to eliminate all of the confounding. 11 Q. For example, a traditional statistical 12 technique that doesn't control for those factors would 13 be the Cox model that was used here; correct? 14 A. No, I think very clearly they state here 15 that they did adjustments based on these confounding 16 variables, including all the ones we just mentioned. 17 And that said, there's still going to be potential for 18 residual confounding because these patients clearly, as 19 you've pointed out, have higher risk factors at 20 baseline for getting cancer, and so despite trying to 21 make that adjustment -- that's why all of these hazard 22 ratios are called adjusted hazard ratios -- and they go 23 through that in the methods pretty detailed -- and they 24 even adjusted by just a few of them versus all of them</p>	<p style="text-align: right;">Page 305</p> <p>1 Correct? 2 A. I missed where you said we were, but I do 3 remember it saying that, yes. 4 Q. I'm on Page 359, left-hand column, second 5 paragraph. 6 A. Okay, yeah. Uh-huh. 7 Q. Liver cancer is a specific cancer; right? 8 A. Yes, it is. 9 Q. So when you said that NDMA containing the 10 valsartan impurity was not associated with any 11 increased risk in overall cancer or with any specific 12 cancer, that's an incorrect statement; correct? 13 A. When it says any specific cancer, that is 14 inaccurate with respect to the liver finding here. 15 Q. The authors continue where I was reading. 16 "This is interesting, as from a biological perspective 17 liver cancer is the most likely form of cancer to 18 resulting from NDMA contamination." 19 That's, I guess, their viewpoint; correct? 20 A. Yes. Yes. 21 Q. Do you agree with that viewpoint? 22 A. I think that it's an interesting finding, 23 given that that is -- one of the risk factors is that 24 that's where the NDMA is metabolized, in the liver, and</p>
<p style="text-align: right;">Page 304</p> <p>1 to see if there are any major differences, and 2 ultimately there weren't any major differences. 3 But I think that we're agreeing that, 4 despite making all of those adjustments, there could 5 still be residual confounding that, as I mentioned, 6 usually would lead to a signal that's a false positive 7 signal if you don't account for an underlying factor 8 that was there. 9 Q. Let's look for a moment at your report if 10 we could. I'm looking at Page 39. And I think, for 11 the record, I just got a note from Chris that we marked 12 the Gomm study as Exhibit 14, just for the record. 13 If you could look at your report, Page 39. 14 You make a statement in the middle of the page, or a 15 little below the middle of the page. You say, "In 16 other words, taking NDMA containing the valsartan 17 impurity was not associated with any increased risk in 18 overall cancer or with any specific cancer." 19 Do you see that? 20 A. Yes. 21 Q. Looking now at Page 359 of the study, the 22 Gomm study, on the left-hand column. They state in the 23 second full paragraph, "For liver cancer, however, we 24 observed a statistically significant association."</p>	<p style="text-align: right;">Page 306</p> <p>1 that at least in the Keto (ph) studies at very high 2 doses, that's -- they do -- they have been noted to 3 have liver cancers, and that the finding here -- one of 4 many findings that's being looked at -- suggests that, 5 at least at a very, very small effect size. 6 I think that's an interesting signal that 7 comes out of this paper, that as we both mentioned has 8 confounding, could be a positive -- a false positive 9 signal based on not adjusting for a lot of different 10 things that we just talked about. 11 As we talked about earlier, it's an 12 interesting finding. Is it enough to hang your hat on 13 and call definitive, as opposed to this should be 14 assessed in an independent cohort that is looking 15 specifically at this question, as opposed to one of 16 many things? That's how I would frame the finding, but 17 it is in that context something that I would say. 18 The only other thing I would point out is 19 that in other animal models, I think I mentioned 20 earlier, is that the nonhuman primates at very high 21 doses of some of these agents don't show liver cancer 22 and that in the Gomm study, even as we both agreed that 23 there is a hypothetical potential of confounding of 24 some of the non-ZHP agents in the control arm, there</p>

<p style="text-align: right;">Page 307</p> <p>1 are zero liver cancer patients.</p> <p>2 So there are two human epi studies that</p> <p>3 show different things with respect to, say, even just</p> <p>4 liver, and so this is why this is not consistent across</p> <p>5 all the data, even in the human epi data. And so like</p> <p>6 I said in summary, it's interesting. It's something</p> <p>7 that should be followed up and looked at independently,</p> <p>8 but it's not enough to say, okay, this is enough to</p> <p>9 move forward and reject the null hypothesis and go to</p> <p>10 the alternative hypothesis for that specific cancer.</p> <p>11 Q. Could you go to Page 358, please? In the</p> <p>12 right-hand column, the first full paragraph, along the</p> <p>13 same lines as what we just talked about, they state,</p> <p>14 "The analysis of individual cancer types showed a</p> <p>15 significant association between potentially</p> <p>16 NDMA-contaminated valsartan and liver cancer, adjusted</p> <p>17 hazard ratio 1.16."</p> <p>18 Then they give the confidence interval,</p> <p>19 1.03 and 1.31, and a P of zero point -- of .017;</p> <p>20 correct?</p> <p>21 A. Yes.</p> <p>22 Q. Is there significance to a P value in one</p> <p>23 of these analyses?</p> <p>24 A. Yes. If you look at their statistical</p>	<p style="text-align: right;">Page 309</p> <p>1 based on the whole body of the other information that</p> <p>2 we've been evaluating here. That's just how science</p> <p>3 works.</p> <p>4 Q. What's a P value?</p> <p>5 A. The P value, as we talked about earlier,</p> <p>6 is the value with which you set somewhat arbitrarily,</p> <p>7 but has been a convention for decades, at .05, meaning</p> <p>8 that you're willing to accept that what your</p> <p>9 association is in any given study or whatever analysis</p> <p>10 you're performing -- is that less than five percent</p> <p>11 means that you have a less than five percent false</p> <p>12 positive rate of the finding that you're seeing. And</p> <p>13 so the problem with that --</p> <p>14 Q. Doctor, I only asked you what it means. I</p> <p>15 didn't -- I just wanted to ask -- I'm just asking for</p> <p>16 terminology.</p> <p>17 MR. INSOGNA: Adam, don't cut off the --</p> <p>18 MR. SLATER: Yeah. I'm sorry. I don't</p> <p>19 mean to interrupt, but we're trying to use time here,</p> <p>20 so I just wanted to kind of get us on track with that.</p> <p>21 That's all I'm trying to say.</p> <p>22 MR. INSOGNA: Had you finished your</p> <p>23 answer?</p> <p>24 A. I was just going to say -- I had already</p>
<p style="text-align: right;">Page 308</p> <p>1 methods, the last sentence of their electronic method,</p> <p>2 it says that all analyses were performed and considered</p> <p>3 statistically significant for a P value of less than</p> <p>4 0.05, which is what we talked about earlier.</p> <p>5 And so in other words, they're admitting</p> <p>6 they didn't correct for multiple testing in this study,</p> <p>7 and so as we explained earlier, that this is at risk of</p> <p>8 a false recovery rate, there's a false positive rate,</p> <p>9 by looking at multiple things slicing and dicing the</p> <p>10 data multiple different ways, which was appropriate to</p> <p>11 see if there's a signal somewhere.</p> <p>12 And essentially, of all the things</p> <p>13 assessed in just this study, let alone including all</p> <p>14 the things looked at at Gomm, let alone if we're</p> <p>15 looking at the full body of evidence of all the data</p> <p>16 we're looking at here, one signal comes out. You just</p> <p>17 have to be very cautious and skeptical that that's</p> <p>18 real, especially when the effect size is like so small.</p> <p>19 So ultimately I think I've summarized and</p> <p>20 said it many times, is that this has to be followed up</p> <p>21 on and this alone is not enough to just say, okay, I'm</p> <p>22 going to reject the null hypothesis, that there's no</p> <p>23 association with liver cancer, and that I'm going to</p> <p>24 accept that it's truly there, based on this one finding</p>	<p style="text-align: right;">Page 310</p> <p>1 said it before -- that if you look at multiple things</p> <p>2 then, then you have to take that into account because</p> <p>3 then your false positive rate goes up. And you -- by</p> <p>4 chance, you could find something by -- that you're</p> <p>5 calling statistically significant because it's less</p> <p>6 than .05, but you've looked at multiple different</p> <p>7 things, which increases your risk of a false positive</p> <p>8 rate. That's all.</p> <p>9 BY MR. SLATER:</p> <p>10 Q. A P value of .017 means that there's less</p> <p>11 than a two percent chance that that finding is due to</p> <p>12 chance; correct?</p> <p>13 That's what that means statistically;</p> <p>14 correct?</p> <p>15 A. As a standalone assessment of just looking</p> <p>16 at that question, yes. But not in the context of</p> <p>17 looking at multiple different things.</p> <p>18 Q. You disregarded the increased risk for</p> <p>19 colorectal cancer and uterine cancer in Pottsgard</p> <p>20 because they didn't reach statistical significance in</p> <p>21 that study; correct?</p> <p>22 MR. INSOGNA: Object to form.</p> <p>23 A. I criticize -- I didn't criticize them.</p> <p>24 You were asking --</p>

<p style="text-align: right;">Page 311</p> <p>1 BY MR. SLATER:</p> <p>2 Q. I said rejected.</p> <p>3 A. I was trying to explain to you why as a</p> <p>4 scientist we wouldn't look at that with -- we would</p> <p>5 look at that with skepticism that that's a real</p> <p>6 finding, the point estimate, given that there's wide</p> <p>7 confidence intervals and that it's not even closely</p> <p>8 statistically significant and the numbers -- are so</p> <p>9 small. That's a different question altogether.</p> <p>10 Q. My only question is this. The findings of</p> <p>11 increased risk for colorectal cancer and uterine cancer</p> <p>12 in Pottgard did not reach statistical significance,</p> <p>13 and you stated in your report that you don't credit</p> <p>14 those findings as a result of the failure to reach</p> <p>15 statistical significance.</p> <p>16 I understand that correctly; right?</p> <p>17 MR. INSOGNA: Object to form.</p> <p>18 A. In the same way that I rejected that some</p> <p>19 of those look like taking the drug is protective,</p> <p>20 because it goes the other way. That's the risk of</p> <p>21 looking at subgroups, is that you get random</p> <p>22 variations.</p> <p>23 BY MR. SLATER:</p> <p>24 Q. Is the answer to my question yes?</p>	<p style="text-align: right;">Page 313</p> <p>1 limitations we've discussed the last two days?</p> <p>2 MR. INSOGNA: Object to form.</p> <p>3 A. No, that's not true. I mean, that's --</p> <p>4 BY MR. SLATER:</p> <p>5 Q. That's all I asked. It's a yes or no.</p> <p>6 A. No. No. It's clearly negative for the</p> <p>7 prior endpoint, both of them, for any cancer being at</p> <p>8 higher risk. That's the clear answer that's not</p> <p>9 true --</p> <p>10 Q. So now coming back -- all right. New</p> <p>11 question.</p> <p>12 So in Pottgard, colorectal cancer,</p> <p>13 uterine cancer, increased risks are shown but not</p> <p>14 reaching statistical significance, and that's one of</p> <p>15 the reasons why you say, "I don't think there's an</p> <p>16 increased risk"?</p> <p>17 In Gomm, according to the authors in a</p> <p>18 peer-reviewed article that you're saying is one of the</p> <p>19 two most important articles you've reviewed, they do</p> <p>20 find an increased risk for liver cancer reaching</p> <p>21 statistical significance, and your response is, "Well,</p> <p>22 in that case it might be due to chance."</p> <p>23 Do I understand you correctly?</p> <p>24 MR. INSOGNA: Object to form.</p>
<p style="text-align: right;">Page 312</p> <p>1 MR. INSOGNA: Object to form.</p> <p>2 A. Can you repeat the actual question?</p> <p>3 BY MR. SLATER:</p> <p>4 Q. The data showing increased risk for</p> <p>5 colorectal cancer and uterine cancer in Pottgard, you</p> <p>6 in your report made it clear that you did not credit</p> <p>7 that study as establishing any risk for those cancers</p> <p>8 because they did not reach statistical significance;</p> <p>9 correct?</p> <p>10 A. Not exactly, no. Because even if it did,</p> <p>11 if it was a multiple assessment and one out of many</p> <p>12 looked like it as a subgroup, we would not look at that</p> <p>13 with definitive conclusion. That's my point.</p> <p>14 If it was the main analysis which was</p> <p>15 powered for that to limit false positive and false</p> <p>16 negative rates, then that's different. But if it's a</p> <p>17 subgroup and you're looking at multiple different</p> <p>18 subgroups, then that's not the only reason why I</p> <p>19 rejected it. It was clearly not significant. But it's</p> <p>20 also because it was just a small subgroup analysis.</p> <p>21 Q. You said you wouldn't draw any definitive</p> <p>22 conclusions based on that. Is it fair to say you</p> <p>23 wouldn't draw any definitive conclusions one way or the</p> <p>24 other based on Gomm and Pottgard, recognizing all the</p>	<p style="text-align: right;">Page 314</p> <p>1 A. Yes, that would be the scientists'</p> <p>2 impression of that data, is to say we have to be</p> <p>3 cautious with that finding and not conclude that it's</p> <p>4 true.</p> <p>5 BY MR. SLATER:</p> <p>6 Q. We also need to as a scientist say that</p> <p>7 could also be very meaningful and could be an important</p> <p>8 signal that this contamination did cause cancer to</p> <p>9 people?</p> <p>10 That's also something you have to take</p> <p>11 into account if you're using an objectively reasonable</p> <p>12 methodology; right?</p> <p>13 MR. INSOGNA: Object to form.</p> <p>14 A. Yes, I've acknowledged that, that that is</p> <p>15 something that you would not ignore, and that you would</p> <p>16 have to follow up on in independent studies and see if</p> <p>17 you're seeing a consistent outcome, which many times</p> <p>18 the problem is -- and which sort of emphasizes what I'm</p> <p>19 trying to say -- is that it doesn't.</p> <p>20 And so as an example, we have another</p> <p>21 study that was done that showed no liver cancers in</p> <p>22 either group that we're talking about that maybe have</p> <p>23 some contamination of the -- into the control arm with</p> <p>24 some of these agents, and there's still no liver</p>

<p style="text-align: right;">Page 315</p> <p>1 cancers. So now we have discrepant data not even 2 consistent from these two studies. 3 BY MR. SLATER: 4 Q. The two studies that you're relying on as 5 over and above all the other evidence in the case have 6 conflicting results; right? 7 MR. INSOGNA: Object to form. 8 A. They have results that are very consistent 9 with random variation when you keep looking at data 10 multiple times, yes. 11 BY MR. SLATER: 12 Q. If we could put that aside for now. Bear 13 with me for a second. I'm trying to tidy up over here 14 for a moment. 15 You mentioned something yesterday that I 16 want to come back to. You said -- well, rephrase. 17 Yesterday I asked you about whether or not 18 it would be ethical to study in a randomized double 19 blind study, the gold standard-type study, study people 20 getting the valsartan that was contaminated at the 21 levels we've seen and have another group of people that 22 gets confirmed uncontaminated valsartan and to run a 23 study. 24 Remember we talked about that yesterday?</p>	<p style="text-align: right;">Page 317</p> <p>1 confirmed with regard to every single pill that the 2 NDMA was well below the acceptable daily limit set by 3 the FDA. 4 Do you recall seeing that in that study? 5 A. I do. 6 Q. And they actually stated levels of 6.3 7 nanograms, 7.5 nanograms, and 10.5 nanograms. 8 Do you remember seeing that? 9 A. I do. 10 Q. And all they were studying in that study 11 was whether or not taking those pills would increase 12 the level of urinary excretion of NDMA; right? That 13 was the endpoint; correct? 14 A. The endpoint was to evaluate whether 15 changes in the NDMA levels in the urine, yes. 16 Q. So coming back to my question, can you 17 imagine any IRB in the United States approving a study 18 where the valsartan pills sold in the United States by 19 Teva that are confirmed to be contaminated at the 20 levels we've seen of NDMA and NDEA would be given to 21 study participants on one side of the study and other 22 people would get valsartan that they know is not 23 contaminated, follow the people for some number of 24 years while they take it, then follow them out for 30</p>
<p style="text-align: right;">Page 316</p> <p>1 A. Yes. 2 Q. And I asked you about running such a study 3 to evaluate the risk of cancer in humans from exposure 4 to that NDMA, and we talked about that; correct? 5 A. Yes. 6 Q. And you said you thought there was a study 7 you had seen where that was actually done I think with 8 Zantac or something similar was done with Zantac. 9 Remember you said that yesterday? 10 A. Yeah, I said that in response to -- your 11 question is, would it be ethical to give a product that 12 was thought to be having an issue such as this to 13 patients prospectively and randomize them? And that 14 was an example of a study that did just that. 15 Q. The JAMA article you're talking about is 16 Florian (ph); right? Or do you not know the author's 17 name? 18 A. It sounds familiar. It was in June of 19 2021. 20 Q. 18 participants who were given Zantac a 21 handful of times over the course of about a month. 22 Does that ring a bell? 23 A. That's right. 24 Q. And that the people who ran the study</p>	<p style="text-align: right;">Page 318</p> <p>1 years to see how many people get cancer? 2 Can you imagine that any IRB in the 3 country would find that to be an ethical study? 4 MR. INSOGNA: Object to form. 5 A. And let me come back, because it's 6 important to answer your question, because you haven't 7 looked at the whole part of that study -- the other 8 study they were talking about with ranitidine or 9 Zantac. And that is that in that storyline, one of the 10 issues is that the ranitidine gets degraded 11 endogenously after being eaten and may be affected by 12 different foods, et cetera, and that study took that 13 into account and was looking at where the levels 14 actually are far higher -- that's the hypothesis -- 15 compared to the exogenous, which is very relevant here 16 actually, too, with nitrosamines. 17 And so it's not only the exogenous amount 18 that they're talking about in NDMA -- of NDMA in the 19 Zantac, but it's also all of the complication that 20 happens upon degradation, which is one of the issues at 21 hand with Zantac. And that study was doing just that 22 and randomizing the different diets even to evaluate if 23 different diet could affect that. 24 And all of those hypotheses were being</p>

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1 tested there in a setting where it possibly could cause
2 cancer, and they did it prospectively in a randomized
3 fashion and it was not deemed unethical. And so the
4 same question now that you're asking me, I can say is
5 that if it was asking a question prospectively and it
6 was -- and analyzing such as question as this to see if
7 something that we don't know for sure is -- we don't
8 have evidence here that says that this at these levels
9 are clearly associated with cancer and someone was
10 doing a prospective study that was well-designed, then
11 I think it would be difficult to do in this setting,
12 but it has been done in an analogous situation already.
13 I don't know what would happen in another
14 proposed study and whether an IRB would accept it or
15 not, but you asked me if it could be and I'm giving you
16 an example where that exact thing was done in an
17 analogous storyline. That's all.
18 BY MR. SLATER:
19 Q. So you have no opinion on my situation
20 about whether that could be done; correct?
21 MR. INSOGNA: Object to form.
22 A. I don't know, which I think was my answer
23 yesterday, too.
24 BY MR. SLATER:

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1 Q. By the way, one question just to close the
2 loop on Zantac. It's been proven that it actually
3 doesn't increase the levels of NDMA in the body; right?
4 It -- the Zantac itself doesn't get
5 somehow activated to create more NDMA? That was a
6 hypothesis that it doesn't appear to have been proven;
7 right?
8 A. The hypothesis was whether or not taking
9 the ranitidine would increase urine excretion or not
10 depending on diet changes, and they did --
11 Q. And they didn't; right?
12 A. And they didn't see any changes in the
13 urinary excretion.
14 Q. Now, if I can find my notes, we'll turn to
15 the Hidajat study for a few moments. That's apparently
16 a big if.
17 MR. SLATER: And Chris, I'm going to
18 assume you're going to mark this as Exhibit 15.
19 Correct me if I'm wrong.
20 [Exhibit 15 marked for identification.]
21 BY MR. SLATER:
22 Q. Now, looking at your report also
23 concurrent with looking at the Hidajat study -- because
24 you talk about it on Page 43 of your report; correct?

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1 A. Yes.
2 Q. If you took a scale and you said, all
3 right, I have to put evidence that I'm looking at on
4 one side or the other pro or con to whether or not NDMA
5 can increase the risk for cancer in humans on one side
6 and saying on one side yes and on the other side no,
7 the Hidajat study would go on the yes side; right?
8 A. As a simple answer, I would say there are
9 so many problems with this paper in terms of putting it
10 on the yes side that although on the surface say the
11 conclusion is that there's an association, when you
12 look at the numerous problems with saying that with
13 respect to the question we're asking today, it would be
14 a soft yes.
15 It would -- when you're weighing the data
16 and looking at all of the evidence, that would not play
17 a large role into saying -- for the question I've been
18 asked -- in terms of the impurities found in valsartan
19 at the trace levels that they've been found, if they
20 increase the cancer. In that question on the yes/no
21 side, it would be a very -- there's also weight on how
22 much was on each side -- it would be very, very low.
23 Q. You certainly wouldn't put the Hidajat
24 study in the no side; right?

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1 A. No. I agree with that.
2 Q. You talked about the limitations and
3 confounders.
4 You talk about that on Page 43; right?
5 A. Yes.
6 Q. I'm not asking you to list them, but did
7 you find any strengths of this study -- anything about
8 it that you would say, yes, this was a good part of the
9 study?
10 MR. INSOGNA: Object to form.
11 A. The positives I guess would be that
12 they're making an effort to try and evaluate a
13 question.
14 BY MR. SLATER:
15 Q. Pull out the Hidajat study for a moment.
16 Page 225 if you -- 255, I should say.
17 And do you see the column that talks about
18 the exposure levels of NDMA?
19 A. The column that talks about exposure
20 level --
21 Q. In the middle?
22 A. Yes. Okay.
23 Q. And are the exposure levels listed from
24 lowest to highest?

<p>Page 323</p> <p>1 A. Yes.</p> <p>2 Q. Is each exposure above the baseline</p> <p>3 associated with a statistically significant increase in</p> <p>4 the rate of cancer?</p> <p>5 MR. INSOGNA: Object to form.</p> <p>6 A. The way you asked that question, they all</p> <p>7 have less than -- less than P values that would call</p> <p>8 them statistically significant, yes.</p> <p>9 BY MR. SLATER:</p> <p>10 Q. Am I also correct that the higher the</p> <p>11 exposure, the higher the cancer risk, according to this</p> <p>12 table?</p> <p>13 A. Yes.</p> <p>14 Q. So does that mean there was a</p> <p>15 statistically significant dose response relationship?</p> <p>16 A. In that focused question, without taking</p> <p>17 all the confounding into account, yes.</p> <p>18 Q. When NDMA is inhaled, is it metabolized?</p> <p>19 MR. INSOGNA: Object to form.</p> <p>20 BY MR. SLATER:</p> <p>21 Q. In the human body?</p> <p>22 A. I think studies that demonstrate or</p> <p>23 evaluate the pharmacokinetics of this agent that don't</p> <p>24 take it orally, which as I think we talked about</p>	<p>Page 325</p> <p>1 A. Yeah. Yes.</p> <p>2 Q. Did they perform a Monte Carlo analysis?</p> <p>3 A. I don't know. I'd have to look.</p> <p>4 Q. Do you know what a Monte Carlo is?</p> <p>5 A. I do not.</p> <p>6 Q. Go to Page 257, please.</p> <p>7 A. Okay.</p> <p>8 Q. If you look at Page 257, the left column,</p> <p>9 the second-to-last paragraph. It's a long paragraph,</p> <p>10 and what they say about halfway down that paragraph,</p> <p>11 they state, "To obtain some indication of the possible</p> <p>12 confounding effect of smoking in this cohort, we used a</p> <p>13 statistical external adjustment method."</p> <p>14 Do you see that?</p> <p>15 A. I do.</p> <p>16 Q. They say, "External Monte Carlo analyses</p> <p>17 based on information on smoking prevalence, ex-smokers,</p> <p>18 and never-smokers from a cohort of rubber industry</p> <p>19 entrants after 1982 indicated that mean bias is only</p> <p>20 1.6 percent compared with the general population." And</p> <p>21 they go on and then they conclude suggesting that</p> <p>22 confounding by smoking in this cohort was likely not a</p> <p>23 significant confounding factor.</p> <p>24 Do you see that?</p>
<p>Page 324</p> <p>1 earlier where it's absorbed, it goes through the portal</p> <p>2 system, it goes to the liver.</p> <p>3 In analyses that looked at what happens if</p> <p>4 it goes through a different route, in fact it gets</p> <p>5 metabolized mostly in the liver also despite that,</p> <p>6 because eventually it gets there, and most of it</p> <p>7 gets eva -- gets metabolized -- and that's where the</p> <p>8 enzyme, the P450 enzyme, exists at that concentration</p> <p>9 that do that, but the answer is yes, eventually that</p> <p>10 would do that.</p> <p>11 Q. So inhaled NDMA would be metabolized in</p> <p>12 the liver; correct?</p> <p>13 A. Eventually.</p> <p>14 Q. You mentioned in your analysis of the</p> <p>15 study that there was a lack of individual smoking data,</p> <p>16 and I think you said that the authors made no effort to</p> <p>17 control for smoking history.</p> <p>18 Do I understand that correctly?</p> <p>19 A. Where do you say that, just so I can read</p> <p>20 it?</p> <p>21 Q. It's on Page 43 in the second paragraph,</p> <p>22 about five lines up, where you say, "Finally the</p> <p>23 Hidajat study made no effort to control for smoking</p> <p>24 history."</p>	<p>Page 326</p> <p>1 A. Yes, I recall reading this. Yes.</p> <p>2 Q. So they did attempt to control for</p> <p>3 smoking; correct?</p> <p>4 A. Well, I guess the way I was reading that</p> <p>5 is that they didn't have smoking exposure from these</p> <p>6 people in this cohort, so what they did was they tried</p> <p>7 to extrapolate from other data to see how that might</p> <p>8 play a role, but I think we've established through all</p> <p>9 of the studies, whether you like them or not, whether</p> <p>10 they're positive or negative, particularly a study like</p> <p>11 this with so many confounding variables, that it's</p> <p>12 nearly impossible to adjust for all of them. They can</p> <p>13 make an effort, but I think we would have to agree that</p> <p>14 this is trying to mitigate a huge problem in the</p> <p>15 analysis.</p> <p>16 Q. You stated that the Hidajat study made no</p> <p>17 effort to control for smoking history. That's what you</p> <p>18 stated in your report.</p> <p>19 That's an inaccurate statement; correct?</p> <p>20 A. They weren't able to get smoking histories</p> <p>21 of the patients that they were analyzing, is what I was</p> <p>22 meaning by that statement. They didn't have it, so</p> <p>23 they couldn't adjust for it, and they had no -- they</p> <p>24 didn't make an effort to get smoking history from those</p>

<p style="text-align: right;">Page 327</p> <p>1 patients.</p> <p>2 Q. Your report says that the study made no</p> <p>3 effort to control for smoking history. Just looking at</p> <p>4 those words, you would agree with me that they did</p> <p>5 attempt to control for smoking; correct?</p> <p>6 A. They did this analysis from patients</p> <p>7 that -- from other patients that weren't these actual</p> <p>8 patients, making a huge assumption.</p> <p>9 Q. Well --</p> <p>10 A. But they didn't account for their own</p> <p>11 patients. They didn't --</p> <p>12 Q. You don't know -- just to be clear, you</p> <p>13 said you're not sure what a Monte Carlo analysis is;</p> <p>14 right?</p> <p>15 A. I don't know the details of the</p> <p>16 statistical measures, but I -- which is what you were</p> <p>17 asking me, and I don't -- but assuming they did that</p> <p>18 properly, this is an assumption from people that aren't</p> <p>19 even the people they're talking about in this study.</p> <p>20 Q. It's a statistical tool that was used in a</p> <p>21 peer-reviewed article and you didn't mention it at all</p> <p>22 in your report?</p> <p>23 Is that a true statement?</p> <p>24 A. I didn't mention this part of the</p>	<p style="text-align: right;">Page 329</p> <p>1 Q. Coming back to my question, if one were to</p> <p>2 come to your report not having the same background we</p> <p>3 all have, not being so familiar with all this material,</p> <p>4 and just read that sentence, finally, the Hidajat study</p> <p>5 made no effort to control for smoking history, that</p> <p>6 would be misleading in the sense that it would suggest</p> <p>7 they ignored the issue when in fact we know they</p> <p>8 actually did a statistical analysis to address it and</p> <p>9 drew a conclusion on that; correct?</p> <p>10 MR. INSOGNA: Object to form.</p> <p>11 A. I answered already that I didn't put every</p> <p>12 point on either side in here. I was pointing out a</p> <p>13 major problem that they don't have the patients'</p> <p>14 smoking history in this analysis.</p> <p>15 BY MR. SLATER:</p> <p>16 Q. Is my statement a true statement?</p> <p>17 MR. INSOGNA: Object to form.</p> <p>18 A. No.</p> <p>19 BY MR. SLATER:</p> <p>20 Q. In order to give a more fair and</p> <p>21 balanced -- well, rephrase.</p> <p>22 In order to give a balanced view of the</p> <p>23 issue of smoking, it would have been appropriate to</p> <p>24 state in your report what the authors did with regard</p>
<p style="text-align: right;">Page 328</p> <p>1 analysis, no.</p> <p>2 Q. All you said in your report is they made</p> <p>3 no effort to control for smoking history. In order to</p> <p>4 be balanced, wouldn't it have made sense to say they</p> <p>5 did a Monte Carlo analysis and state what they found so</p> <p>6 at least you could show both sides and show that they</p> <p>7 did make an effort to address smoking and didn't just</p> <p>8 ignore it?</p> <p>9 MR. INSOGNA: Objection. Form.</p> <p>10 MR. KUM: Objection. Form.</p> <p>11 MR. INSOGNA: Compound. Argumentative.</p> <p>12 A. I didn't mention every point on every</p> <p>13 article about every thing. My summaries here of this</p> <p>14 paper are pointing out the many, many limitations of</p> <p>15 this study, which was used heavily by plaintiff experts</p> <p>16 to look at a question that is far removed from what</p> <p>17 this study is looking at.</p> <p>18 So I didn't put that there. I could</p> <p>19 have -- I -- we could go through this paper and I could</p> <p>20 have missed some of the things that would negate this</p> <p>21 even further. I was just pointing out a few examples</p> <p>22 of how this is severely confounded and has so many</p> <p>23 significant problems with the question at hand here.</p> <p>24 BY MR. SLATER:</p>	<p style="text-align: right;">Page 330</p> <p>1 to smoking; correct?</p> <p>2 MR. INSOGNA: Object to form.</p> <p>3 A. I was pointing out highlights of this</p> <p>4 paper in terms of significant limitations.</p> <p>5 BY MR. SLATER:</p> <p>6 Q. In your report on Page 43, in the middle</p> <p>7 of that second paragraph -- bear with me for one</p> <p>8 second. Ah.</p> <p>9 On Page 43 of your report, in the second</p> <p>10 paragraph, about two-thirds of the way down, you say,</p> <p>11 "Moreover, the Hidajat study used estimations of NDMA</p> <p>12 exposure based on job title and air quality</p> <p>13 measurements associated with those job titles, while</p> <p>14 also assuming study participants remained in the same</p> <p>15 position throughout their careers. That is a</p> <p>16 significant and in my view implausible assumption and</p> <p>17 makes the estimations inherently questionable."</p> <p>18 That's what you stated in your report;</p> <p>19 right?</p> <p>20 A. Yes, I see that.</p> <p>21 Q. Now, look at Hidajat, if you could, Page</p> <p>22 251, top right-hand corner of the page under the</p> <p>23 heading exposure assessment. Halfway down that</p> <p>24 paragraph it says, "Because only job information in</p>

<p style="text-align: right;">Page 331</p> <p>1 1967 was available, the primary analyses assumed all 2 subjects remained in the same factory department -- 3 i.e., not necessarily in the same job -- throughout 4 their careers and were employed until retirement at age 5 70, death, or emigration." 6 Do you see that? 7 A. Yes. 8 Q. So when you said in your report that 9 Hidajat assumed everybody stayed in the same position, 10 that was incorrect because they explicitly said they 11 did not assume people stayed in the same job; right? 12 A. They stayed in the same department, same 13 position in the department. 14 Q. You said that they will -- you said in 15 your report -- you referred specifically to job titles, 16 and then you said while also assuming study 17 participants remained in the same position. 18 You were referring when you said same 19 position to the same job? That's what you meant; 20 right? 21 A. In the same department, as it states here. 22 Q. But that's not what your report says, 23 because you didn't say that? 24 A. Where --</p>	<p style="text-align: right;">Page 333</p> <p>1 to different departments, and to assume that they 2 wouldn't is a huge assumption; that's all. 3 In fact, let me just characterize -- of 4 all the limitations in this study, I think that that's 5 the least important, actually. Of all of the 6 limitations, which include all of the exposures to all 7 of these other known carcinogens, Type 1 carcinogens in 8 many cases, that are inhaled, not even orally ingested 9 here, that are -- this is the bigger issue with this 10 paper in terms of confounders, to ask the question 11 about -- we're not even -- we're talking about NDMA at 12 trace levels in a pill that's taken for a few years, as 13 opposed to over decades exposure here to so many 14 different carcinogens. 15 It's really -- I mean, it's an extension, 16 it's a surrogate of surrogate of surrogates, trying to 17 look at a question, and of all the evidence we've 18 talked about so far, this is the least evidence -- the 19 least weight evidence that I would put on this one. 20 BY MR. SLATER: 21 Q. Just to be clear, you're not claiming to 22 be an expert on whether people would stay in the same 23 department in the rubber industry in the United 24 Kingdom?</p>
<p style="text-align: right;">Page 332</p> <p>1 Q. I mean, let's look at your report. You 2 say, "Moreover, the Hidajat study used estimations of 3 NDMA exposure based on job title and air quality 4 measurements associated with those job titles while 5 also assuming study participants remained in the same 6 position throughout their careers." 7 You're obviously when you say same 8 position talking about the job title; right? 9 MR. INSOGNA: Object to form. 10 A. And the job titles would be grouped by 11 department; okay? So I'm not being as specific as you 12 would like, and I think that clearly it states here 13 that they stayed in the same department, which is what 14 the meaning of this was, to clarify. 15 BY MR. SLATER: 16 Q. Well, you said that is a significant and 17 in my view implausible assumption and makes the 18 estimations inherently questionable, the suggestion 19 that someone would stay in the same job for all those 20 years. 21 But it's certainly not implausible that 22 someone would stay in the same department, is it? 23 MR. INSOGNA: Object to form. 24 A. It's an assumption, and people move around</p>	<p style="text-align: right;">Page 334</p> <p>1 You don't have any knowledge or expertise 2 in that field at all, would you? 3 A. Nor would I say that they most definitely 4 all stayed in the same department. I mean, it's my 5 assumption. That is -- I think we're both agreeing on. 6 Q. My question is this. You're not stating 7 that you have some expertise or any special knowledge 8 about whether people would stay in the same position or 9 not or the same department or not; right? 10 A. I don't have special expertise other than 11 just common sense, that that's just an assumption that 12 that not necessarily is true. 13 Q. Do you know what the departments were in 14 the United Kingdom in the rubber industry during the 15 time this study was being conducted? 16 Do you know what the departments were 17 called? 18 A. No. 19 Q. Do you know how many departments there 20 were? 21 A. No. 22 Q. Do you know if there may be two 23 departments in the whole factory? 24 A. No, although that's not what it sounds</p>

<p style="text-align: right;">Page 335</p> <p>1 like here as they're calling it more of a -- multiple 2 different potential departments. 3 Q. You have absolutely no idea how many 4 departments there would have been in any of these 5 factories; right? 6 A. No. 7 MR. INSOGNA: Object to form. 8 A. Nor does it matter in the grander context, 9 as I've already mentioned. 10 BY MR. SLATER: 11 Q. Do you know if people in that industry in 12 that time period saw these jobs as jobs for life and 13 would settle into a department and make that their job 14 for life and would work until they either died or 15 stopped working? 16 Do you know if that's how it worked back 17 then? 18 MR. INSOGNA: Object to form. 19 A. I don't know. It's possible. 20 BY MR. SLATER: 21 Q. You have no idea; right? 22 MR. INSOGNA: (Inaudible) possible. 23 BY MR. SLATER: 24 Q. You have no idea; right?</p>	<p style="text-align: right;">Page 337</p> <p>1 more of a gold standard to ask a question and minimize 2 as many biases as possible. I already mentioned that 3 there have been similar studies in analogous cases, but 4 I will agree that it's difficult to do randomized 5 studies for various reasons and one of them is it's 6 challenging to do and to coordinate. 7 But that doesn't mean that we should then 8 rely solely on evidence that's not good and just say, 9 well, we're going to do that instead and just agree and 10 believe it. We have to look at it skeptically; that's 11 all. 12 BY MR. SLATER: 13 Q. Do you know what the tobacco industry and 14 their experts were saying early on about the quality of 15 the studies that people were saying proved that tobacco 16 caused cancer? 17 Do you know what they were saying at that 18 time? 19 MR. INSOGNA: Object to form. 20 A. I don't know -- 21 BY MR. SLATER: 22 Q. Would it surprise you to find out that 23 basically were saying the -- they were saying the same 24 thing -- let me rephrase.</p>
<p style="text-align: right;">Page 336</p> <p>1 A. Not relevant and not -- 2 MR. INSOGNA: Object -- 3 A. And potentially possible. 4 BY MR. SLATER: 5 Q. In your report you mentioned on Page 43 6 the Straif study from 2000; right? 7 A. Yes. 8 Q. That study also found statistically 9 significant increased risks for multiple cancers; 10 correct? 11 A. Yes, with the exact similar confounding 12 problem and limitations as Hidajat. Also that -- 13 Q. Do you think that it's difficult to study 14 the risk to humans from exposure to NDMA because of the 15 limitations on how you can set up studies for whether 16 or not you can give NDMA to humans, for example, as 17 we've talked about, and because of just how the world 18 works? 19 Is it just hard to set up a study that you 20 would say, "That's a great study. That can answer the 21 question"? 22 MR. INSOGNA: Object to form. 23 A. It relates to the question about 24 prospective randomized study, which of course would be</p>	<p style="text-align: right;">Page 338</p> <p>1 Would it surprise you to learn that the 2 tobacco industry was basically making the same 3 arguments that we're hearing from you and the 4 manufacturers of the contaminated valsartan back then? 5 MR. INSOGNA: Objection. 6 MR. KUM: Objection. That assumes facts 7 not in evidence. 8 MR. INSOGNA: Same objection. 9 MR. SLATER: Wait. I'm sorry. Let me 10 just -- before you answer, Doctor. Did somebody just 11 object and say that it assumes facts not in evidence? 12 This is a deposition. We're not putting anything into 13 evidence till we get to trial, counsel. 14 Am I missing something, or do -- would you 15 like to maintain that objection? 16 MR. KUM: Well you're making an assertion 17 without laying a foundation for it, so -- 18 MR. SLATER: Okay. Assumes facts not in 19 evidence. Okay. 20 BY MR. SLATER: 21 Q. Doctor, you can answer the question. 22 A. Can you repeat it for me, please? 23 Q. Sure. Would it surprise you to learn that 24 the tobacco industry made very similar arguments to</p>

<p style="text-align: right;">Page 339</p> <p>1 what we're hearing here in defense of these valsartan 2 cases with regard to the risks of cancer from smoking? 3 MR. INSOGNA: Same objections. 4 BY MR. SLATER: 5 Q. Same type of thing? We don't have RCTs. 6 We have to -- you can't rely on animal models. 7 Short-term studies. We're not seeing a lot of effects 8 on these short-term studies of people who smoked. 9 Would it surprise you to hear that all the 10 same arguments were basically being made to defend the 11 tobacco industry? 12 A. My response to that is, is that science 13 always will tell the truth if it's done properly, and 14 what you're calling tobacco -- that's a Type 1 15 carcinogen, and we know that, and there's evidence to 16 support that, and the data was done to do that. 17 We're asking here now, do we have enough 18 evidence to say that? And I'm telling you the answer 19 is no, there's not enough evidence to say that. That's 20 all I'm saying. 21 Q. Do you know that the experts for the 22 tobacco industry said exactly the same thing that 23 you're saying here when they were defending tobacco 24 before it was recognized widely around the world to be</p>	<p style="text-align: right;">Page 341</p> <p>1 risk of cancer? 2 And we have some cohorts that actually 3 were looking at exactly that with the exact pills and 4 controlled in some ways -- everyone was taking 5 valsartan, et cetera. We already talked about some of 6 the confounding that's residual in those studies. But 7 those studies are negative. 8 And now we have a whole body of studies 9 that are based on looking at exposures in the 10 occupational setting to in this case rubber workers 11 that have exposure to so many other carcinogens that 12 it's nearly impossible to account for that are looking 13 at extensions of the question at hand here at doses 14 probably far higher than what we're talking about in 15 these trace levels in the pills. 16 Then it's not like I'm not looking at it 17 or I'm not considering it, but it's certainly not 18 anywhere near the level of where I'm putting weight on 19 this particular question at hand. It's not enough -- 20 Q. So -- 21 A. -- that these studies are positive to 22 say, okay, so we can move on now and establish that not 23 only is there an association, but now it's causing the 24 cancer.</p>
<p style="text-align: right;">Page 340</p> <p>1 a dangerous carcinogen for humans? 2 MR. INSOGNA: Object -- 3 A. That's irrelevant. From a scientific 4 perspective of my -- what I'm asked to do, we are 5 asking if we can reject the null hypothesis, which 6 is -- you have to start from that -- there is no 7 association, there is no causation -- and prove it to 8 me that there is with a body of evidence. 9 So you can't equate that and this which 10 has completely different storylines. There's not 11 enough body of evidence to make that call at this 12 point. Both can be true, in other words. 13 BY MR. SLATER: 14 Q. In terms of your methodology, does Hidajat 15 even figure into the analysis, or do you just say this 16 is a study I don't have to really consider because of 17 the issues I've seen, so I don't even take it into 18 consideration? 19 A. I think I mentioned yesterday that when 20 you're looking at a question like this, you have to 21 consider all available evidence and weigh it. And we 22 have evidence looking at the actual question that was 23 asked of me, which is, do these pills that have trace 24 levels, very small levels of this agent, increase the</p>	<p style="text-align: right;">Page 342</p> <p>1 Q. Well, I probably can save us a bunch of 2 time right now perhaps with a couple questions based on 3 what you said, because I think I'm getting a good idea 4 of what your understanding is. 5 There's obviously a lot of dietary studies 6 that you've looked at and analyzed; right? 7 A. Yes. 8 Q. You talk about them in your report; right? 9 A. Yes. 10 Q. You would agree that there are dietary 11 studies that support the proposition that NDMA 12 increases the risk and actually causes cancer in humans 13 and there are some studies that were not definitive on 14 that question or that you might even say support your 15 opinion; right? 16 MR. INSOGNA: Object to form. 17 A. You're using the word risk, but I think I 18 would use associations that have been positive or 19 negative, depending on various studies. And -- 20 BY MR. SLATER: 21 Q. I'll use your vocabulary. Let me ask 22 again. 23 You would agree that there are dietary 24 studies that support a significant association and</p>

<p style="text-align: right;">Page 343</p> <p>1 there are studies that don't or are not definitive one 2 way or the other; right? 3 MR. INSOGNA: Object to form. 4 A. There are studies that have shown positive 5 associations and others that haven't in looking at the 6 same cancer type and looking at other cancer. In fact, 7 most of the studies that expert plaintiffs rely on 8 don't mention anything about diet causing hepatic or 9 liver cancers, which is the whole focus of the human 10 epi data, and we're not talking about it. We're 11 talking about gastric cancer and other colon cancer 12 over here in the diet. 13 So this is an example of, okay, it's all 14 over the place and there's no consistent story, and so 15 when I'm looking at this to say is there enough 16 evidence to change me from the null hypothesis -- 17 alternative -- about any -- about all cancers, the 18 answer is no. And if I'm looking at a specific cancer, 19 there's no consistent trend throughout any of this 20 either. 21 And so, yes, the dietary sub -- back to 22 your question -- has some for and some against, but 23 it's very non -- it's inconsistent, and it's not 24 something one could rely on given all the other</p>	<p style="text-align: right;">Page 345</p> <p>1 established that NDMA does not increase the risk for 2 cancer or cause cancer in humans; correct? 3 A. That's not how science works, but 4 certainly any of the data that is reliable or the more 5 reliable data, the answers have been no in those 6 reports. In other words, there was no association in 7 Gomm and all cancers. There's no association in 8 Pottegard and all cancers. But that's not how -- I'm 9 not trying to prove that it doesn't cause based on the 10 scientific approach. 11 Scientific approach is to start with the 12 hypothesis that there's no difference with this and I 13 need to prove that there is based on some sort of 14 evidence, and there is no such evidence to do so. 15 Q. I just -- the reason I asked the question 16 is because, as you understand, I have to go through 17 what your opinions are. I didn't see an opinion saying 18 that the evidence proves it doesn't increase the risk 19 or cause cancer. 20 That's not an opinion you've drawn, it's 21 not what you've done here; right? 22 A. That's not the opinion I'm stating 23 explicitly. 24 Q. There's some discussion in your report</p>
<p style="text-align: right;">Page 344</p> <p>1 confounding issues with the diet stuff that I've 2 mentioned in my report. 3 BY MR. SLATER: 4 Q. If I understand your opinion ultimately -- 5 and please correct me if I'm wrong, even though I know 6 you're shy about saying that -- 7 A. That was sarcastic. 8 Q. I'll start over. I'll start over. 9 Tell me if I understand. Based on your 10 review of everything, you looked at everything and you 11 weighed it as you weighed it and you came up with a 12 conclusion. Your conclusion is the evidence is not 13 sufficient to establish that the exposure of 14 individuals to the valsartan with the NDMA and the NDEA 15 levels in the pills that were actually sold in the 16 United States increased or cau -- the risk for 17 cancer -- or caused cancer to humans? 18 Your position is the evidence is not 19 sufficient to say yes to that, and that's your opinion; 20 right? 21 A. That's my opinion, yes. 22 Q. Your opinion is not that the evidence 23 proves that the answer is no? You're not taking the 24 position that, based on the evidence, it's been</p>	<p style="text-align: right;">Page 346</p> <p>1 about endogenous formation of NDMA. 2 You've looked at that and commented on it 3 in your report, that subject; right? 4 A. Yes. 5 Q. Again, I'm trying to be good with our time 6 right now, so I'm going to try to cut to the chase with 7 some things. 8 I did not see -- an opinion as to some 9 level of endogenous formation of NDMA that you have 10 said, "Based on my review of the literature, this is 11 what's being formed in the human body and I ascribe to 12 this model and I think this is the right amount"? 13 You haven't formed that opinion; correct? 14 MR. INSOGNA: Object to form. 15 BY MR. SLATER: 16 Q. Was that question convoluted? 17 A. A little bit, but I -- my summary -- 18 Q. Let me just ask it cleaner. I'm sorry. I 19 didn't mean to interrupt. Because counsel objected, 20 and he's probably right on that one. Let me ask it 21 again. 22 I did not see in your report an opinion as 23 to an assumed rate or quantification of endogenous 24 nitrosamine formation in the human body.</p>

<p style="text-align: right;">Page 347</p> <p>1 You didn't form an opinion on that 2 question; right? 3 A. I didn't calculate a rate on my own, no. 4 Q. You didn't, for example, adopt a specific 5 article and say this is the model I think is the right 6 one, so this is the one I'm going with? 7 That's not an opinion you have that you've 8 drawn in this case; right? 9 MR. INSOGNA: Object to form. 10 A. And to summarize that part of the -- my 11 report and my review of the literature on that is that 12 you're looking at various studies, that there is a 13 known endogenous rate and that the levels, although 14 they range depending on how they're calculated in given 15 authors and different papers, they're high. 16 They're much higher on orders of magnitude 17 than what we're talking about even just with 18 exogenous diet, and when we're talking about sort of 19 the FDA limit, the ADI, and the amounts that are in 20 these actual pills. 21 So that's the sort of general 22 understanding from the diet endogenous formation that I 23 take from it in this -- to short -- the argument that 24 we are exposed to very high levels of this daily, so</p>	<p style="text-align: right;">Page 349</p> <p>1 terms of my comments on endogenous and how I just told 2 you how I used that in formulating the opinion, the 3 task at hand, that's it. 4 BY MR. SLATER: 5 Q. The studies that talk about endogenous 6 formation and actually try to quantify it -- there's a 7 range of different figures they come up with; right? 8 A. There is a range. 9 Q. And would you agree that there's no 10 scientifically accepted consensus as to how to 11 calculate endogenous NDMA? 12 Would you agree that's still an open 13 question? 14 A. I think that there is probably room for 15 refining the calculation, but as I'm using it, all of 16 the available calculations have estimated levels far 17 higher than the levels we're talking about here at 18 hand. So -- 19 Q. Did you see -- well, all right. This is, 20 I guess, coming back to my question, though. 21 You certainly aren't giving the opinion 22 that there's some scientific consensus as to how to 23 calculate endogenous NDMA formation? 24 There's multiple people that have</p>
<p style="text-align: right;">Page 348</p> <p>1 that this is a big problem in terms of saying that now 2 this little trace amount in a pill is going to change 3 what we're already exposed to at such high levels 4 inherently through routine living. 5 So that's why, again, we come back to 6 look -- some of the studies where they find 7 associations with cancer is when they take into account 8 endogenous versus exogenous, it's the endogenous part 9 in the calculation that looks like there's the 10 association, not based on the exogenous component in 11 the diet. 12 BY MR. SLATER: 13 Q. Coming back to my question, you didn't 14 adopt any of these studies in your opinions and say 15 that's the right model, that's the right way to 16 calculate it, that's the right amount; right? 17 MR. INSOGNA: Object to form. 18 BY MR. SLATER: 19 Q. I'm just making sure I didn't miss it in 20 your report. I didn't see it. I just want to make 21 sure it's not an opinion you drew in your report; 22 that's all. 23 MR. INSOGNA: Same objection. 24 A. Other than what you read in the report in</p>	<p style="text-align: right;">Page 350</p> <p>1 different approaches, but there's no scientific 2 consensus on this; right? 3 A. I would -- I don't know that literature as 4 well as whether or not there's scientific consensus, 5 but I know that there are some studies that even 6 attempted to do analysis through different ways to come 7 up with this and show a range, all, again, very high, 8 much higher than what we're talking about here, and 9 consistent with the overall sort of global picture that 10 the endogenous levels take up the majority of this 11 issue and that a minuscule component is the exogenous 12 component, and so many of these dietary studies that 13 don't take that into account aren't addressing that 14 part -- that confounding issue. 15 Q. The studies are basing their estimates on 16 mathematical models; right? 17 A. I believe that they are. Some are 18 measuring directly surrogates of exposure, et cetera, 19 but yes. 20 Q. For example, you'll acknowledge that 21 certain nitrosamines can be measured and you can figure 22 out to some extent what's coming out of the body, but 23 NDMA, for example, is metabolized and you can't really 24 measure what would be formed in the body; right?</p>

<p style="text-align: right;">Page 351</p> <p>1 MR. INSOGNA: Object to form.</p> <p>2 A. There are -- I mean, there are the three</p> <p>3 ways, if I can pull up my --</p> <p>4 BY MR. SLATER:</p> <p>5 Q. Or do you not know? You can say I don't</p> <p>6 know and then I move on.</p> <p>7 MR. INSOGNA: Object to form.</p> <p>8 A. Can I -- I want to point out one area in</p> <p>9 my report just so that I state it correctly, if I can</p> <p>10 find it. The Hrudy (ph) study, which is -- okay.</p> <p>11 Right.</p> <p>12 So I was just making sure that I got the</p> <p>13 three ways in the Hrudy study that were used</p> <p>14 simultaneously to sort of look at the range that was</p> <p>15 identified, and so some of them are actually just</p> <p>16 measuring NDMA levels directly in the blood.</p> <p>17 And so if you're quantifying how much,</p> <p>18 say, for example, you're exogenously taking and you</p> <p>19 could compare how much is in the blood, you can</p> <p>20 estimate how much was endogenously created. And so</p> <p>21 your question of you can't accurately do that -- not</p> <p>22 necessarily true.</p> <p>23 You could estimate the exogenous exposure</p> <p>24 with the limitations that that has, which are far</p>	<p style="text-align: right;">Page 353</p> <p>1 than the exogenous levels in the diet.</p> <p>2 BY MR. SLATER:</p> <p>3 Q. Did you see any studies that estimated the</p> <p>4 level of endogenous formation of NDMA at not what you'd</p> <p>5 consider to be very high levels?</p> <p>6 A. There were a range, I think, as we talked</p> <p>7 about, at various extremes, but even at the lowest</p> <p>8 levels they were higher -- much higher than, say, the</p> <p>9 FDA ADI, as an example.</p> <p>10 Q. Well, for example, did you see any studies</p> <p>11 that estimated the level at perhaps 1,000 nanograms a</p> <p>12 day?</p> <p>13 A. I believe that 1,000 nanograms a day,</p> <p>14 which is about 100 times the 96 nanograms that the FDA</p> <p>15 has indicated as an acceptable level, so that's my</p> <p>16 point, is that there are orders of magnitude even at</p> <p>17 the lowest estimates. That's all I'm saying.</p> <p>18 So I think in the end I'd agree with you</p> <p>19 that I'm not here to opine on what's the appropriate</p> <p>20 way to do it, but I'm looking at all of the body of</p> <p>21 literature that's talking about endogenous formation,</p> <p>22 how to calculate it, and the range -- the lower level</p> <p>23 of the range is far higher, let alone probably the more</p> <p>24 likely is about -- the actual true way of doing it is</p>
<p style="text-align: right;">Page 352</p> <p>1 lower, and then evaluate how much is in the blood and</p> <p>2 deduce that there's endogenous creation, because it's</p> <p>3 much higher in the blood than what you've estimated</p> <p>4 that was being taken externally.</p> <p>5 BY MR. SLATER:</p> <p>6 Q. You're saying that's one potential</p> <p>7 approach, but you're not giving an opinion to a</p> <p>8 reasonable degree of scientific certainty that that's</p> <p>9 the accurate approach; right?</p> <p>10 MR. INSOGNA: Object to form.</p> <p>11 A. You asked me if it's possible and what's</p> <p>12 the rationale of it, and it's been done and shows that,</p> <p>13 yes.</p> <p>14 BY MR. SLATER:</p> <p>15 Q. But you agree with me you're not reaching</p> <p>16 an opinion that, for example, the Hrudy model is the</p> <p>17 right one and the other models are wrong? You're just</p> <p>18 saying this is one person who came up with this way to</p> <p>19 do it and you're pointing it out?</p> <p>20 Do I understand correctly?</p> <p>21 MR. INSOGNA: Object to form.</p> <p>22 A. There are multiple ways to do it and I</p> <p>23 tried to show that there are various ways to do it and</p> <p>24 that overall the answer is always that it's much higher</p>	<p style="text-align: right;">Page 354</p> <p>1 above that.</p> <p>2 Q. Are you saying that 1,000 nanograms a day</p> <p>3 of intake of NDMA would be a very high level?</p> <p>4 A. No, I'm saying it's a lot higher than 96</p> <p>5 nanograms, which was the FDA's accepted daily intake.</p> <p>6 And this is on routine daily living. That's -- I think</p> <p>7 that's the point.</p> <p>8 Q. Just to come back to my question --</p> <p>9 because I got to know how far we have to go and if I</p> <p>10 have to go start picking up articles in the other</p> <p>11 room -- you're not offering an opinion that there's a</p> <p>12 certain level of endogenous formation -- you're saying</p> <p>13 this is the level that I'm assuming is formed?</p> <p>14 You're just telling me there are studies</p> <p>15 that have measured it with various methods at various</p> <p>16 levels; correct?</p> <p>17 MR. INSOGNA: Object to form.</p> <p>18 A. Yes, other than what we've already</p> <p>19 mentioned in my previous responses.</p> <p>20 BY MR. SLATER:</p> <p>21 Q. I need to understand this. I didn't see</p> <p>22 an opinion in your report where you quantified an</p> <p>23 assumption as to the level of endogenous formation of</p> <p>24 NDMA in the human body.</p>

<p>Page 355</p> <p>1 You're not offering a specific opinion as</p> <p>2 to a specific level; right?</p> <p>3 MR. INSOGNA: Object to form.</p> <p>4 A. No, other than the ranges that I put in my</p> <p>5 report.</p> <p>6 BY MR. SLATER:</p> <p>7 Q. And when you refer to the ranges in your</p> <p>8 report, you're pointing out that there are different</p> <p>9 models and different ranges have been presented and</p> <p>10 that's as far as you're going in terms of quantifying</p> <p>11 endogenous formation; right?</p> <p>12 A. Yes.</p> <p>13 Q. And you also hold out the -- for the --</p> <p>14 rephrase.</p> <p>15 You also agree with me that these models</p> <p>16 may all be wrong and it may turn out the levels are</p> <p>17 much lower; right?</p> <p>18 MR. INSOGNA: Object to form.</p> <p>19 A. There's no evidence about that. We're</p> <p>20 always happy to evaluate new data. That's how science</p> <p>21 works. But currently the data suggests that this is</p> <p>22 the way to do it, that the levels are extremely high.</p> <p>23 BY MR. SLATER:</p> <p>24 Q. You don't have an opinion as to what the</p>	<p>Page 357</p> <p>1 right?</p> <p>2 MR. INSOGNA: Object to form.</p> <p>3 A. That's not what I'm using endogenous</p> <p>4 amounts for.</p> <p>5 BY MR. SLATER:</p> <p>6 Q. I'm not asking about endogenous. I'm</p> <p>7 asking you --</p> <p>8 A. I'm telling you -- you're asking if 1,000</p> <p>9 nanograms per microgram -- if 1,000 nanograms per day</p> <p>10 is a high level?</p> <p>11 Q. In a pill of valsartan.</p> <p>12 MR. INSOGNA: I'm sorry. I missed the</p> <p>13 question.</p> <p>14 BY MR. SLATER:</p> <p>15 Q. I'll ask it again. Let me -- we'll start</p> <p>16 over.</p> <p>17 Do you agree that 1,000 nanograms of NDMA</p> <p>18 in a valsartan pill would be a high exposure?</p> <p>19 MR. INSOGNA: I just want to make sure I'm</p> <p>20 clear. You're saying 1,000 nanograms, is your</p> <p>21 question?</p> <p>22 MR. SLATER: Yes.</p> <p>23 A. A high exposure relative to what?</p> <p>24 Relative to the FDA level that's high --</p>
<p>Page 356</p> <p>1 level of endogenously-formed NDMA is in the human body?</p> <p>2 You don't have an opinion as to a specific</p> <p>3 level, do you?</p> <p>4 MR. INSOGNA: Object to form. Vague.</p> <p>5 A. Not other than what I've put in my report</p> <p>6 that there's a range that's very high compared to the</p> <p>7 question at hand here and the questions at hand, no.</p> <p>8 BY MR. SLATER:</p> <p>9 Q. Your opinion is that there's a potential</p> <p>10 range and that potential range may have some high</p> <p>11 figures in it, but you're not saying, "In my opinion,</p> <p>12 this is the right number," because you haven't</p> <p>13 evaluated that issue or calculated it; right?</p> <p>14 A. I'm not saying that it's one number. I'm</p> <p>15 not saying it's a potential range. It is a clear range</p> <p>16 that's been reported in the literature of a high --</p> <p>17 very high amount and then the low end is still high</p> <p>18 compared to the levels we're talking about at the FDA</p> <p>19 level. There is a clear range -- not a potential</p> <p>20 range. It's a range that we see in the literature.</p> <p>21 Q. If a valsartan pill had 1,000 nanograms of</p> <p>22 NDMA in it -- let me start over.</p> <p>23 If a valsartan pill had 1,000 nanograms of</p> <p>24 NDMA in it, you would agree that's a high exposure;</p>	<p>Page 358</p> <p>1 BY MR. SLATER:</p> <p>2 Q. You just said 1,000 nanograms would even</p> <p>3 be a high level of NDMA. I'm asking, does that hold</p> <p>4 true when it's in a pill sold by the people that hired</p> <p>5 you?</p> <p>6 Is it still a high level if it's in the</p> <p>7 pill from the people that hired you?</p> <p>8 MR. INSOGNA: Object to form.</p> <p>9 Misstates --</p> <p>10 BY MR. SLATER:</p> <p>11 Q. Or does it now become a low level because</p> <p>12 they're responsible for it?</p> <p>13 MR. INSOGNA: Object to form. Misstates</p> <p>14 his testimony.</p> <p>15 A. I'm trying to tell you that through</p> <p>16 routine living we have high levels -- 1,000 nanograms</p> <p>17 is at the lowest estimate of that -- just from living</p> <p>18 and eating, and that these levels are extremely higher</p> <p>19 than what the FDA has shown, has reported, or has put</p> <p>20 out as a threshold of what's safe. That's all I'm</p> <p>21 saying.</p> <p>22 And so what you're asking now, is an extra</p> <p>23 1,000 nanograms a lot? No, not in the context of that</p> <p>24 sea of exposure that we're exposed to all the time just</p>

<p style="text-align: right;">Page 359</p> <p>1 from endogenous calculation of that. That's my point. 2 BY MR. SLATER: 3 Q. So you're -- well, my question was, is 4 1,000 nanograms of NDMA in a valsartan pill sold by the 5 manufacturers that hired you a high exposure in and of 6 itself? 7 MR. INSOGNA: Object to form. 8 A. No, it is not a high exposure when taking 9 into account how high of exposures we are every day to 10 just routine living, no. 11 BY MR. SLATER: 12 Q. So no big deal? Take 1,000 nanograms of 13 NDMA in your pills every day and it's no big deal? 14 Is that your opinion? 15 MR. INSOGNA: Object to form. Misstates 16 the testimony. 17 A. I was asked to -- whether or not that that 18 made any difference, and I think I have opined many 19 times that there's no evidence that it is. Now we're 20 asking about that in relation to the routine daily 21 exposures to this same chemical, and it's trivial in 22 the end compared to what we are all the time, and so 23 the answer is no. 24 Now, would I take it on purpose? That's a</p>	<p style="text-align: right;">Page 361</p> <p>1 risk; right? 2 MR. INSOGNA: Object to form. 3 A. There would be no reason to do that. 4 BY MR. SLATER: 5 Q. You'd be adding potential risk and no 6 benefit; correct? 7 MR. INSOGNA: Object to form. 8 A. There would be adding no known benefit and 9 we don't have any evidence that it would be adding any 10 risk. 11 BY MR. SLATER: 12 Q. You think there's no evidence in the world 13 that that would be adding potential risk? 14 MR. INSOGNA: Object to form. 15 A. I think that's the question that we've 16 been asked that we've been talking about, and I think I 17 opined very clearly that there's no evidence to support 18 that hypothesis and changing from the alternative 19 hypothesis -- the alternative hypothesis, no. 20 BY MR. SLATER: 21 Q. Isn't really what you're saying is there's 22 evidence, but because of my evaluation of that 23 evidence, I don't believe the evidence is persuasive? 24 That's really what you're saying; right?</p>
<p style="text-align: right;">Page 360</p> <p>1 different question that's not relevant to what I'm 2 being asked at the moment. 3 BY MR. SLATER: 4 Q. Is that not a question -- then that's not 5 the question you were asked to answer here in this case 6 as an expert; right? 7 A. What? Whether I'd want to take a pill of 8 valsartan? No, nobody asked me that -- to -- my 9 comment on that. 10 Q. Well, the question of whether or not -- 11 you said it'd be a different question of whether or 12 not -- and when you said would I want to take it, I 13 took that as would a person want to take it or would 14 you want to give that to your patients. 15 The answer to that would be no; right? 16 MR. INSOGNA: Object to form. Vague. 17 BY MR. SLATER: 18 Q. We went through that yesterday. The 19 answer would be no; right? 20 A. Yeah. To answer that question, I'd say 21 there's no added benefit of adding that to the pill 22 over what already the benefit is of that pill, so there 23 would be no point in taking it. 24 Q. All you would be entertaining is potential</p>	<p style="text-align: right;">Page 362</p> <p>1 A. The body of evidence available to us does 2 not allow us to reject the null hypothesis that there's 3 no association with these added trace elements to the 4 alternative hypothesis that there is a clear, not only 5 association, but actual causation of this in terms of 6 cancer. No, there is not enough evidence to make that 7 assertion. 8 Q. And that's based on your evaluation of the 9 evidence, which you understand other people have looked 10 at and formed different conclusions on the same 11 evidence; right? 12 MR. INSOGNA: Object to form. 13 A. I'd have to disagree with that, because I 14 think if I am correct, Dr. Etmenan (ph) didn't even 15 talk about the human epi data, at least that I could 16 see in the report. So maybe they made some conclusion, 17 but they didn't look at even all of the evidence that I 18 think's available to us. 19 BY MR. SLATER: 20 Q. If someone didn't look at all the evidence 21 that is available and relevant to the question, that 22 would indicate a flawed methodology; right? 23 MR. INSOGNA: Object to form. 24 A. If you're not looking at the most</p>

<p style="text-align: right;">Page 363</p> <p>1 important elements, which I think, as we've 2 established, are the human epi data, looking at the 3 actual question at hand, then that would be quite 4 problematic if you're coming up with an answer without 5 even taking that into account. 6 MR. INSOGNA: Adam, are you at a point 7 where we can take a break? 8 MR. SLATER: Sure. Let's take 10. Off 9 the record. 10 THE REPORTER: Okay. James? 11 THE VIDEOGRAPHER: Going off the record. 12 THE REPORTER: We are going off the record 13 at 1:47 PM. 14 [A brief recess was taken.] 15 THE VIDEOGRAPHER: We are back on the 16 record at 2:05 PM. 17 BY MR. SLATER: 18 Q. Let's look at Page 44 of your report, 19 please. 20 This is the page where you talk about 21 animal studies; correct? 22 A. Yes. 23 Q. At the bottom of the page, you state, "On 24 the other hand, while animal studies are of limited</p>	<p style="text-align: right;">Page 365</p> <p>1 Q. Coming back to what I asked you, you 2 confirmed yes, that's your opinion in terms of how the 3 animal studies fit into this case; right? 4 MR. INSOGNA: Object to form. 5 BY MR. SLATER: 6 Q. That the animal studies do not prove that 7 the actual exposures in the valsartan pills here over 8 the period of time that these pills were actually taken 9 by people would not cause cancer in humans? 10 Is -- am I understanding your opinion on 11 the issue of how the animal studies fit in? 12 MR. INSOGNA: Same objection. 13 A. At -- yes, at those levels that I'm 14 looking at in those animal studies, they're not 15 supportive of the question at hand. 16 BY MR. SLATER: 17 Q. In the animal studies where NDMA was being 18 deliberately given to the animals -- and it was; right? 19 They were deliberately giving it to the animals; right? 20 A. Yes. 21 Q. They were giving it deliberately to the 22 animals to cause cancer; right? 23 A. They were evaluating whether it would 24 cause cancer, yes, and titrating up the levels in</p>
<p style="text-align: right;">Page 364</p> <p>1 utility in extrapolating data to draw firm conclusions 2 about human carcinogenesis, none of the animal studies 3 relied upon by plaintiffs' experts demonstrates that 4 exposure to the levels of NDMA demonstrated to exist in 5 certain valsartan medications would be capable of 6 causing cancer when administered over the brief period 7 that the impurity existed in those medications." 8 That's what you wrote; right? 9 A. Yes. 10 Q. And if I understand correctly, what you're 11 saying is you can't use the animal studies to establish 12 that exposure to the NDMA levels in the actual pills 13 over the actual period of time that they were taken 14 would have been sufficient to cause cancer in the 15 people who are claiming cancer was caused. 16 Do I understand that correctly? 17 A. Yes, and the reason for that is because 18 the levels at which -- depending on which study you 19 look at -- but the levels at which they are causing 20 cancers in the animal models are at much, much higher 21 levels than what we're talking about in these trace 22 levels in the valsartan pills. 23 And so that's what that summary is 24 alluding to.</p>	<p style="text-align: right;">Page 366</p> <p>1 different cohorts, and evaluating at which point were 2 they starting to see cancers, was there a dose 3 relationship, et cetera, and at what level did they 4 start seeing cancers above basal rates in the control 5 group not getting NDMA, which would be a good way to 6 evaluate that question. 7 Q. NDMA is actually given deliberately to 8 laboratory animals to give them cancer so that they can 9 then be studied once they get diagnosed with cancer; 10 right? 11 A. Well, now that studies that we were just 12 referring to have established that at certain doses you 13 can elicit a cancer, then the following questions would 14 be okay, now we can use that as models to study cancer, 15 to treat it, to evaluate it, et cetera. Yes, you would 16 have to know the dose at which to elicit it. In other 17 words, if you're underdosing them, they never get the 18 cancer. 19 And so the answer to your question is yes, 20 though. Now that that was identified, they can use 21 those doses. 22 Q. When these large doses are given, the 23 intent is to give cancer to these animals and to do it 24 quickly?</p>

<p>Page 367</p> <p>1 That's the goal; right?</p> <p>2 MR. INSOGNA: Object to form.</p> <p>3 A. In a model that you're referring to where</p> <p>4 you're trying to get a cancer so that now you can study</p> <p>5 the cancer, sure, you'd want to try and elicit the</p> <p>6 cancer quickly.</p> <p>7 BY MR. SLATER:</p> <p>8 Q. You rely -- and I think you might have</p> <p>9 mentioned it, unless I was hearing things -- to certain</p> <p>10 studies done with monkey animal models; correct?</p> <p>11 A. Yes.</p> <p>12 Q. And I think that there's two in particular</p> <p>13 by Adamson.</p> <p>14 You're familiar with those studies, you're</p> <p>15 relying on them; correct?</p> <p>16 A. Yes.</p> <p>17 Q. And one involved seven monkeys, and the</p> <p>18 other involved six monkeys.</p> <p>19 Does that sound right?</p> <p>20 A. Yes.</p> <p>21 Q. Are you aware of what Dr. Adamson's view</p> <p>22 is on the subject of the risk to humans of exposure to</p> <p>23 NDMA?</p> <p>24 MR. INSOGNA: Object to form.</p> <p>Page 368</p> <p>1 A. I don't know what his view is, or his</p> <p>2 opinions.</p> <p>3 MR. SLATER: Chris, let's put up the</p> <p>4 editorial from "The Oncologist," titled "The Finding of</p> <p>5 N-Nitrosodimethylamine in Common Medicines."</p> <p>6 And I think -- are we up to Exhibit is it</p> <p>7 16 or 17?</p> <p>8 THE REPORTER: I believe it's 16.</p> <p>9 MR. SLATER: Hearing nothing to the</p> <p>10 contrary, I will mark mine as 16.</p> <p>11 [Exhibit 16 marked for identification.]</p> <p>12 BY MR. SLATER:</p> <p>13 Q. Have you seen this editorial authored by</p> <p>14 Dr. Adamson?</p> <p>15 A. I have not.</p> <p>16 MR. SLATER: Chris, if we could, could you</p> <p>17 go to Page 461 of this article, please? And go to the</p> <p>18 right-hand side of the page, and let's just go to the</p> <p>19 bottom right paragraphs.</p> <p>20 There's a paragraph three from the --</p> <p>21 third from the bottom that says, "Aside from their role</p> <p>22 as complete carcinogens, the nitrosamines are likely to</p> <p>23 be cofactors or promoters in patients with underlying</p> <p>24 hepatic damage due to alcoholism, hepatitis, or hepatic</p>	<p>Page 369</p> <p>1 steatosis."</p> <p>2 A. Where is he?</p> <p>3 BY MR. SLATER:</p> <p>4 Q. Third paragraph from the bottom of the</p> <p>5 right-hand column.</p> <p>6 A. Right. Okay.</p> <p>7 Q. Were you aware that Dr. Adamson authored</p> <p>8 an editorial offering that viewpoint?</p> <p>9 A. I wasn't aware of that, but that viewpoint</p> <p>10 doesn't mean that it's true, if that's your question.</p> <p>11 Q. I'm just asking if you're aware that he</p> <p>12 said that in this editorial.</p> <p>13 A. No, I didn't.</p> <p>14 Q. Because you've drawn certain conclusions</p> <p>15 based on his studies on monkeys that you don't believe</p> <p>16 that we can show that NDMA would increase the risk for</p> <p>17 cancer to humans, so I thought it might be helpful to</p> <p>18 show you some -- an editorial that the author of those</p> <p>19 studies authored last year addressing his viewpoints.</p> <p>20 I just was curious if you had seen this.</p> <p>21 You haven't seen that; right?</p> <p>22 A. I hadn't seen that, and when you asked me</p> <p>23 if I relied on his paper, I relied on the data from his</p> <p>24 paper, not on his opinions in that paper or here.</p> <p>Page 370</p> <p>1 Q. Looking at the bottom right-hand</p> <p>2 paragraph, it states, "In conclusion, NDMA</p> <p>3 contamination poses a potential carcinogenic risk of</p> <p>4 undetermined effect at present for those taking</p> <p>5 ranitidine, valsartan, or related medications on a</p> <p>6 regular basis. It is thus incumbent upon industry and</p> <p>7 the FDA to take steps to identify and eliminate the</p> <p>8 sources of contamination of medications with this class</p> <p>9 of carcinogen."</p> <p>10 You would agree with that statement;</p> <p>11 right?</p> <p>12 MR. INSOGNA: Object to form.</p> <p>13 A. I don't disagree with anything in that</p> <p>14 statement suggesting that there are possibil -- these</p> <p>15 are the questions that we're asking now, and we alluded</p> <p>16 to this in a similar scenario where you asked earlier,</p> <p>17 that during the time that we're making an evaluation,</p> <p>18 you want to make an effort to not continue that</p> <p>19 exposure, but that doesn't confirm that there is a true</p> <p>20 risk.</p> <p>21 All of his words are very carefully</p> <p>22 chosen. You see "poses a potential risk," that we have</p> <p>23 to look at this to see if it's actually real. But none</p> <p>24 of this is saying that this is a definitive problem, et</p>
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<p style="text-align: right;">Page 371</p> <p>1 cetera, et cetera.</p> <p>2 So you're right, I don't disagree with</p> <p>3 that language to say that we have to sort of look into</p> <p>4 it and evaluate if there's a risk or not. That's what</p> <p>5 we're doing now, and that's what I did, and found no</p> <p>6 association.</p> <p>7 BY MR. SLATER:</p> <p>8 Q. And did you see any articles in your --</p> <p>9 MR. SLATER: You can take this down,</p> <p>10 Chris. I'm through with that article.</p> <p>11 BY MR. SLATER:</p> <p>12 Q. Did you see any literature that would</p> <p>13 support the viewpoint that NDMA can cause cancer in</p> <p>14 monkeys?</p> <p>15 A. Cancer in general?</p> <p>16 Q. Did you see any published articles in the</p> <p>17 peer-reviewed literature concluding that NDMA given to</p> <p>18 monkeys can cause cancer in those monkeys, or other</p> <p>19 primates, for that matter?</p> <p>20 A. NDMA I think in the papers I referenced</p> <p>21 and saw didn't.</p> <p>22 Q. For example, did you see any article in</p> <p>23 the peer-reviewed literature that concluded that their</p> <p>24 data supports epidemiology implicating nitrosamines in</p>	<p style="text-align: right;">Page 373</p> <p>1 not aware of a study that utilized NDMA with monkeys</p> <p>2 and concluded that the data supported epidemiology</p> <p>3 implicating nitrosamines in causation of cancers of</p> <p>4 stomach and other organs?</p> <p>5 You didn't see any such literature in your</p> <p>6 review?</p> <p>7 MR. INSOGNA: Object to form. If you're</p> <p>8 going to quote from a document, I believe the witness</p> <p>9 is entitled to review the document you're quoting from.</p> <p>10 MR. SLATER: I'm asking if he saw anything</p> <p>11 like that in his work to prepare his report and form</p> <p>12 his opinions. It's a simple question, yes or no.</p> <p>13 MR. INSOGNA: Object to form.</p> <p>14 MR. SLATER: Counsel, I'm not putting the</p> <p>15 document up. Please stop interrupting me so I can</p> <p>16 finish this deposition now.</p> <p>17 BY MR. SLATER:</p> <p>18 Q. Yes or no? Did you see any such article,</p> <p>19 Doctor?</p> <p>20 A. I didn't see that in my research. I'm</p> <p>21 always happy to look at new data and analyze it if it</p> <p>22 comes available.</p> <p>23 Q. So in forming your opinions that the --</p> <p>24 that studies on monkeys establish the viewpoint that</p>
<p style="text-align: right;">Page 372</p> <p>1 causation of cancers of stomach and other organs in</p> <p>2 alcohol as enhancing internal exposure to nitrosamines?</p> <p>3 Did you see any article indicating that?</p> <p>4 MR. INSOGNA: Object to form.</p> <p>5 A. So you're asking nitrosamines, not NDMA.</p> <p>6 So that's a different question, and I didn't see that</p> <p>7 specifically, but I wasn't looking for nitrosamines</p> <p>8 specifically. I was looking for NDMA.</p> <p>9 BY MR. SLATER:</p> <p>10 Q. The language I just read to you came from</p> <p>11 a study regarding NDMA. I'm just letting you know</p> <p>12 that.</p> <p>13 So I'm asking you, did you see a study</p> <p>14 that studied NDMA with primates or monkeys specifically</p> <p>15 where it was concluded that the data supported</p> <p>16 epidemiology implicating nitrosamines in this study</p> <p>17 they actually studied NDMA and ethanol co-exposure --</p> <p>18 I'm sorry. I got to start over. I mixed up sentences.</p> <p>19 MR. INSOGNA: Counsel, if you're reading</p> <p>20 from a document, do you want to put it on the screen so</p> <p>21 he can follow --</p> <p>22 MR. SLATER: No, I don't. I don't.</p> <p>23 BY MR. SLATER:</p> <p>24 Q. Let me -- Doctor, just to be clear, you're</p>	<p style="text-align: right;">Page 374</p> <p>1 NDMA would not be causing an increased risk to humans,</p> <p>2 you didn't take into account any study in which an</p> <p>3 actual conclusion was able to be drawn that based on a</p> <p>4 study of monkeys there would be a risk to humans?</p> <p>5 You didn't see any such study, you took</p> <p>6 none into account; correct?</p> <p>7 MR. INSOGNA: Object to form.</p> <p>8 A. I didn't see that study that you're</p> <p>9 referring to. I'd be happy to look at it and evaluate</p> <p>10 its -- how it adds to the body of literature.</p> <p>11 BY MR. SLATER:</p> <p>12 Q. One of the things we touched on yesterday</p> <p>13 was documents that were internal to the manufacturers</p> <p>14 of these contaminated pills.</p> <p>15 Remember we talked about that a little bit</p> <p>16 yesterday?</p> <p>17 A. Yes.</p> <p>18 Q. If any such documents were authored by</p> <p>19 people within those companies that, for example, were</p> <p>20 toxicologists whose job it was to evaluate the risk of</p> <p>21 this exposure to nitrosamines, you would have wanted to</p> <p>22 see that; right?</p> <p>23 MR. INSOGNA: Object to form. Incomplete</p> <p>24 hypothetical.</p>

<p style="text-align: right;">Page 375</p> <p>1 A. More evidence and more data are always 2 important. I relied on the available evidence to me to 3 make an analysis to see about the question at hand 4 here. 5 So more evidence and more data are always 6 welcome to put into the analysis. 7 BY MR. SLATER: 8 Q. Documents showing the opinions and 9 viewpoints of toxicologists who either worked for the 10 manufacturers or were consulted by the manufacturers 11 regarding the risk to humans of the NDMA contamination 12 from your perspective would be certainly something of 13 potential significance that you would have wanted to 14 see; right? 15 MR. INSOGNA: Object to form. 16 A. Similar to the opinions of other 17 investigators that you pointed out. I mean, opinions 18 are not data, and I am looking at data to make my own 19 opinion, not rely on someone, what they felt or wrote 20 or said about something. That would not sway my 21 analysis here. 22 Data, on the other hand, is a different 23 thing. 24 BY MR. SLATER:</p>	<p style="text-align: right;">Page 377</p> <p>1 I don't know how that would play a role 2 into my decision here. Would I want to look at it if 3 there was something available? Of course. 4 BY MR. SLATER: 5 Q. You'd want to see it, because as you said 6 regarding methodology, if there's something of 7 potential significance, to have a valid methodology 8 you'd need to at least take it into account; right? 9 MR. INSOGNA: Object to form. Incomplete 10 hypothetical. 11 A. I don't know what the evidence or data is 12 you're talking about to even say if it was something 13 that should be included in my analysis to begin with. 14 BY MR. SLATER: 15 Q. Would the viewpoints of the manufacturers, 16 their internal knowledge of the risk -- and we're 17 talking the companies that actually were selling the 18 pills and were required by law to understand the risks 19 and benefits. 20 If they had viewpoints on this and had 21 analyzed this situation, that certainly could 22 potentially have been significant to you; right? 23 MR. INSOGNA: Object to form. Asked and 24 answered.</p>
<p style="text-align: right;">Page 376</p> <p>1 Q. If toxicologists who were familiar with 2 the pills and the NDMA and what it is and the risk who 3 actually worked for these companies evaluated this 4 situation, you certainly would want to see their 5 evaluation; right? 6 MR. INSOGNA: Object to form. Asked and 7 answered yesterday. 8 A. And I think just recently I answered of 9 course I would want to see all evidence and data. 10 BY MR. SLATER: 11 Q. For example, if a toxicologist who worked 12 for Teva said that NDMA is a potent mutagenetic 13 carcinogen and needs to be controlled at subthreshold 14 of toxicological concern levels, you would want to know 15 that toxicologists working at Teva felt that, and you 16 would want to understand why; right? 17 MR. INSOGNA: Object to form. Asked and 18 answered. Incomplete hypothetical. 19 A. I'd want to know all information, how much 20 that would play a role in determining the question I 21 was asked to assess based on available evidence, based 22 on data and investigations, that's -- I don't even know 23 what you're talking about, and you're not telling me 24 the specifics, so it's all vague questionings.</p>	<p style="text-align: right;">Page 378</p> <p>1 BY MR. SLATER: 2 Q. Potentially significant; right? You 3 haven't seen it, so you don't know? 4 A. I don't -- 5 MR. INSOGNA: Object to form. Asked and 6 answered. Incomplete hypothetical. Also, Adam, I 7 thought at the outset you said you were not going to go 8 into liability questions. 9 MR. SLATER: This is not a liability 10 question. This has to do with the risk. These 11 questions all go to the evaluation of the risk of the 12 NDMA and NDEA and the pills that were sold. 13 I'm not talking about avoiding putting the 14 chemical into the pill. That's a different question 15 probably for someone else. 16 BY MR. SLATER: 17 Q. So you would want to -- you certainly 18 would want the lawyers who hired you to have given you 19 this type of information that I'm asking you about so 20 you wouldn't have had to sit here right now saying, "I 21 don't know. I haven't seen any of it. Maybe it would 22 matter, maybe it wouldn't. I don't know?" 23 You'd prefer to have seen it; right? 24 MR. INSOGNA: Object to form.</p>

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<p>1 A. I don't know how that would have played a 2 role in my analysis, because I don't know what you're 3 talking about. 4 BY MR. SLATER: 5 Q. If one of the manufacturers took the 6 position that the NDMA that was found in the valsartan 7 pills presented an unacceptable carcinogenic risk to 8 the intended patient population, you certainly would 9 want to know that; right? 10 MR. INSOGNA: Same objections. 11 A. Similar to the previous answer is 12 someone's opinion is different than what the reality is 13 or at least what the data show about that, that 14 specific topic. 15 So I don't know what you're talking about 16 or the details about it, but if it's just an opinion 17 about somebody, it would not necessarily play a role 18 into the actual data analysis that I'm talking about. 19 BY MR. SLATER: 20 Q. What if it was a position taken by the 21 company in a public document that the NDMA in the 22 valsartan that they were selling presented an 23 unacceptable carcinogenic risk to the intended patient 24 population?</p>	<p>1 though, is opinions and statements, but it's not data 2 that would sway me based on the data that we have 3 available. 4 So that's all I can say, based on what 5 you're telling me. 6 BY MR. SLATER: 7 Q. So the analysis and opinions of, for 8 example, toxicologists who worked for or retained by 9 the defendants to specifically evaluate the risks posed 10 by this NDMA to patients is something you're telling me 11 wouldn't really matter to you? 12 MR. INSOGNA: Object to form. Incomplete 13 hypothetical. 14 A. I don't know. I don't know what is 15 involved in this, what you're talking about to even 16 make an opinion on it or state it either way. 17 BY MR. SLATER: 18 Q. Coming back to the monkey studies -- 19 rephrase. 20 Coming back to the animal studies. When 21 the FDA established the acceptable intake limits, it 22 based those limits on studies with rats; correct? 23 A. Yes. 24 Q. And I think -- I don't think it's at my</p>
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<p>1 MR. INSOGNA: Same objections. 2 A. That has no data behind it, and I don't 3 know how that would play a role into the data that 4 we've just talked about that's available to me to 5 review. 6 BY MR. SLATER: 7 Q. You think that a company would take that 8 position without even having any data available to it? 9 MR. INSOGNA: Same objections. Incomplete 10 hypothetical. Argumentative. 11 BY MR. SLATER: 12 Q. Or you just don't know? 13 A. I don't know where that position's coming 14 from. Is it because they found these impurities and 15 they think there's a potential risk and they wanted to 16 mitigate it? 17 I mean, that doesn't tell me that there's 18 a clear association based on data. 19 Q. You would want to know more? You would 20 want to understand the document? But you certainly 21 would want to have the opportunity to consider that; 22 right? 23 MR. INSOGNA: Object to form. 24 A. It sounds like that what you're offering,</p>	<p>1 power, but I want to make sure I covered this. We 2 talked yesterday about the long materials considered 3 list, as opposed to the list of numbered references 4 yesterday in your report. 5 Remember that? 6 A. Yes. 7 Q. And I'm going to be transparent. The 8 reason I'm asking you this is so I don't have to walk 9 study by study through this. 10 I think we established yesterday -- just 11 tell me if I had it right -- if something's on the 12 materials considered list but didn't find its way into 13 the report with a specific reference, it's something 14 that you may have reviewed, may have skimmed it, may 15 have looked at it, but it wasn't so significant that 16 you felt that you needed to actually reference it in 17 the report and rely directly on it; right? 18 MR. INSOGNA: Object to form. 19 A. Yes. 20 BY MR. SLATER: 21 Q. So I wouldn't need to go through all the 22 studies that weren't cited in the report to ask how it 23 was important to you, because if it was important it 24 would have been in the report; correct?</p>

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1 MR. INSOGNA: Object to form.
2 A. I think I mentioned earlier that the
3 references I put in my actual report are token
4 references, representative references on a topic.
5 They're not an exhaustive reference list of every paper
6 that's talked about this topic.
7 BY MR. SLATER:
8 Q. Well, that's not my question, and if your
9 answer is that again, we're going to have to go through
10 all the studies, because I'm not going to leave
11 something significant unturned, so let me just make
12 sure you understand where we're coming from.
13 If there's an article that's listed in the
14 materials considered, but it's not in the report, not
15 specifically referenced, it's not something that you
16 found was so significant to your opinions that you
17 actually specifically referenced it and talked about
18 it; correct?
19 MR. INSOGNA: Same objection.
20 A. For the most part, that's probably true.
21 I think I mentioned one of the papers, which is
22 probably getting to what we're getting at now, which
23 was added later, which was talking about how to
24 establish the dose level and acceptable dose levels.

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1 That one would probably be an important
2 one, because it's a little bit more relevant to the
3 question as hand. But other than that, the majority of
4 them are either accessory and aren't relied upon
5 specifically.
6 BY MR. SLATER:
7 Q. If you had seen something in a study that
8 you felt was of significance, you would have talked
9 about it in the report; right?
10 MR. INSOGNA: Object to form.
11 A. If I had seen it at the time of the
12 report, yes.
13 MR. SLATER: Okay. I have no other
14 questions at this time.
15 MR. INSOGNA: I'm going to have some
16 questions. I don't know about anybody else who's on
17 the line. I'll need a few minutes to organize my
18 notes. So if you want to take maybe 15, and then we
19 can come back.
20 MR. SLATER: Sure.
21 MR. INSOGNA: Okay. Let's say 20. Just I
22 don't want you to tell me I'm late again, but I will
23 work as fast as I can.
24 MR. SLATER: And we're off the record;

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1 right? Let's go off.
2 THE VIDEOGRAPHER: We're going off the
3 record at 2:30 PM.
4 [A brief recess was taken.]
5 THE VIDEOGRAPHER: We are back on the
6 record at 3:08 PM.
7 EXAMINATION
8 BY MR. INSOGNA:
9 Q. So Dr. Catenacci, I have a few questions
10 for you. I think some other attorneys may have a few
11 questions as well. And this is a little bit awkward, I
12 know, because of the remote nature of this deposition.
13 You're on camera, I'm actually sitting next to you.
14 But if you could just continue to look at the camera, I
15 think that will make it somewhat less awkward, and if
16 we have documents, we'll put those up on screen.
17 MR. SLATER: Hey, one quick question
18 before you get started, Nick. Wait --
19 MR. INSOGNA: Yes.
20 MR. SLATER: I don't see -- I don't see
21 you on here.
22 A. On video.
23 MR. SLATER: Your video.
24 MR. INSOGNA: Oh, you're right. You're

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1 right. Let me fix that. Let's pause for a second.
2 Let's just go off the record for one second. I dropped
3 my feed.
4 THE VIDEOGRAPHER: We are going off the
5 record at 3:08 PM.
6 [A brief recess was taken.]
7 THE VIDEOGRAPHER: We are back on the
8 record at 3:12 PM.
9 BY MR. INSOGNA:
10 Q. So Dr. Catenacci, you were asked a number
11 of questions by plaintiffs' counsel yesterday about the
12 nature of the question you were asked to answer in this
13 case.
14 Do you recall those?
15 A. Yes.
16 Q. Have you in the course of this deposition
17 fully described the question that you were intending to
18 address with your report?
19 A. Yes, I think that I was able to get across
20 that I was asked to evaluate whether these trace levels
21 of NDMA in valsartan increased or were associated with
22 cancer in people taking them.
23 And I was able to relay how I went about
24 that, the methodology, and that ultimately after

<p style="text-align: right;">Page 387</p> <p>1 evaluating all the evidence, in terms of the starting 2 point of that there is no association, or null 3 hypothesis, that weighing all the evidence, including 4 the body of evidence we discussed, that there was no 5 such association and that the conclusion was that 6 there's not enough evidence to support the allegation 7 that it was increasing the risk of cancer. 8 Q. And over the course of your work preparing 9 your report in this case, did defendants' counsel 10 attempt to influence your opinions in any way? 11 A. No. 12 Q. Were specific opinions suggested to you? 13 A. No. 14 Q. But plaintiffs' counsel also asked you 15 about your methodology and questions about whether you 16 did an independent review or looked at what plaintiffs' 17 experts cited and then relied on their documents. 18 Do you remember those questions? 19 A. Yes. Yes. 20 Q. Now, as a scientist, when you answer a 21 question like the question you just described for us a 22 moment ago, what's the starting premise for you? 23 A. The starting premise, again, in any 24 scientific question if there's a hypothesis, is what's</p>	<p style="text-align: right;">Page 389</p> <p>1 A. Hundreds. 2 Q. And can you recall, roughly speaking, how 3 much of that review was a result of your searching? 4 A. A majority. 5 Q. Do you feel that the searches you 6 conducted in preparing your report were sufficiently 7 exhaustive to allow you to answer the question as you 8 framed it earlier? 9 A. Yes. 10 Q. Are you aware of additional information or 11 data that would change the opinions you've offered in 12 any way? 13 A. I'm not aware. 14 Q. Earlier today, plaintiffs' counsel asked 15 whether you made any attempt to calculate an acceptable 16 daily intake of NDMA or NDEA; right? 17 A. Right. 18 Q. And I believe that you testified that you 19 did not undertake such an effort; right? 20 A. Correct. 21 Q. Was it necessary for you to calculate an 22 ADI of NDMA or of NDEA in order to offer your causation 23 opinion? 24 A. No.</p>
<p style="text-align: right;">Page 388</p> <p>1 the null hypothesis and what's the alternative, and in 2 order to evaluate that from the standpoint where I had 3 the dataset that was being relied upon to suggest that 4 the alternative hypothesis should be accepted, and I 5 looked at that, because that's the evidence being put 6 forth to try and sway against the null hypothesis. 7 Of course, after evaluating that and 8 looking at that, I looked at the more broader context 9 of all the data available, as we've been discussing, 10 through the routine way that I do research that I've 11 done through my career as a scientist, in terms of all 12 my training and the natural way that one would go about 13 the question like this. 14 So ultimately I looked at those reports 15 from the plaintiffs' experts that they're relying on 16 very closely, because that's what they were relying on, 17 of course, and pointed out, as I mentioned, the 18 limitations of the argument that's being put forward. 19 Q. And when you looked for articles beyond 20 what the plaintiffs were relying on, did you find any? 21 A. Yes. 22 Q. And how many -- just a ballpark, how many 23 articles would you estimate you considered over the 24 course of your review in this case?</p>	<p style="text-align: right;">Page 390</p> <p>1 Q. And if I recall correctly, plaintiffs' 2 counsel's questions were in the context of some FDA 3 publications that discussed FDA's ADI for NDMA; right? 4 A. Yes. 5 Q. Do you know how FDA went about calculating 6 its ADI figure? 7 A. Yes, I think I had mentioned that a few 8 times through the deposition that it was obtained from 9 the rat data, extrapolating from the rat data using a 10 linear analysis, using very high doses of the agent in 11 that preclinical model, and looking at the time point 12 at which half of the rats got cancer, died, and 13 extrapolating backwards. 14 Q. And without yourself doing a calculation 15 of an ADI for NDMA or NDEA, were you able to draw any 16 conclusion or form any opinion about the ADI that FDA 17 set forth in his publications? 18 A. Yeah, it was clearly a low and what I 19 would say conservative estimate, based on I think we 20 talked about just recently all the numbers and levels 21 in the diet and that were endogenous exposures that 22 we're routinely exposed to on a daily basis. 23 So it just -- it looks obviously low 24 compared to these reports.</p>

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<p>1 Q. When you say it looks low compared to 2 these reports, can you explain what it is you mean by 3 that?</p> <p>4 A. It looks like it's at a very low level 5 compared to the levels that we're talking about and 6 that we saw in many of the dietary studies, just 7 talking about the exogenous exposures that we have, let 8 alone the endogenous exposures that we have through 9 just routine daily living.</p> <p>10 And so it seems low compared to what we're 11 routinely exposed to on a daily basis.</p> <p>12 Q. And since you mentioned the endogenous 13 exposure, let me ask you a question about that.</p> <p>14 Plaintiffs' counsel asked you some 15 questions today about whether you calculated a level of 16 endogenous exposure through the course of preparing 17 your report.</p> <p>18 Do you remember those questions?</p> <p>19 A. Yes.</p> <p>20 Q. Did you do an independent calculation of 21 how much endogenous NDMA people are exposed to on a 22 daily basis?</p> <p>23 A. No.</p> <p>24 Q. Would doing an independent calculation of</p>	<p>1 we're talking -- and I was asked about exposures to 2 relatively much smaller levels and potentially for a 3 shorter amount of time in the valsartan products.</p> <p>4 Q. Plaintiffs' counsel also asked you a 5 series of questions about the reasonableness of 6 prescribing or taking a valsartan drug containing a 7 nitrosamine impurity versus prescribing or taking one 8 without it.</p> <p>9 Do you recall those questions?</p> <p>10 A. Yes.</p> <p>11 Q. And your testimony as I see it on the 12 record is that there is no reason to take the drug with 13 the impurity because there's no benefit to it.</p> <p>14 Do you recall that testimony?</p> <p>15 A. Yes.</p> <p>16 Q. Can you explain what you mean by there's 17 no benefit to taking the drug with the impurity?</p> <p>18 A. I meant that there's no added benefit on 19 top of just taking the drug without the impurity. In 20 other words, there's no benefit from the impurity 21 itself.</p> <p>22 In other words, you're still going to get 23 the benefit that you would have gotten -- that it was 24 intended to do, which was an anti-hypertensive</p>
Page 392	Page 394
<p>1 a level of endogenous NDMA or NDEA have influenced your 2 opinions in this case?</p> <p>3 A. No.</p> <p>4 Q. When you reviewed the literature that you 5 relied on in your report, did you see calculations that 6 others had done of endogenous levels of NDMA or NDEA?</p> <p>7 A. Yes.</p> <p>8 Q. And that endogenously formed nitrosamines 9 levels in the studies that you reviewed, how do they 10 compare to exposures from other sources?</p> <p>11 A. From other sources like exogenous, do you 12 mean?</p> <p>13 Q. Correct. How do the endogenous levels 14 that you saw reported in the medical literature compare 15 to the levels in exogenous sources?</p> <p>16 A. They were astronomically higher and dwarf 17 the levels that we have from an exogenous source.</p> <p>18 Q. And how, if at all, did that fact inform 19 your opinions?</p> <p>20 A. Well, we're looking at, as I mentioned, 21 the levels that we're exposed to on a daily basis. 22 They're extremely high at everyday environmental, 23 including the endogenous exposures.</p> <p>24 So that's an important consideration when</p>	<p>1 medication.</p> <p>2 Q. So would taking valsartan containing a 3 nitrosamine impurity still offer a benefit to the 4 patient as a sartan drug?</p> <p>5 A. Yes.</p> <p>6 Q. Is there any evidence of which you're 7 aware that valsartan drugs containing a nitrosamine 8 impurity are any less efficacious for the purpose for 9 which they're prescribed?</p> <p>10 A. Not that I'm aware of, no.</p> <p>11 Q. Do you hold any opinion or have you seen 12 any literature concerning whether a valsartan drug 13 containing a nitrosamine impurity would still work as 14 intended to control hypertension?</p> <p>15 A. I have not seen any evidence to suggest 16 that it wouldn't work the same way that it always 17 would.</p> <p>18 Q. Plaintiffs' counsel asked you some 19 questions yesterday about the Pottegard study; right?</p> <p>20 A. Yes.</p> <p>21 Q. And specifically he asked you whether it's 22 possible that patients in the control arm received 23 valsartan from another manufacturer of the API that was 24 later discovered to have an NDMA or NDEA impurity;</p>

<p style="text-align: right;">Page 395</p> <p>1 right?</p> <p>2 A. Yes.</p> <p>3 Q. Have you seen any evidence in the</p> <p>4 literature anywhere to suggest that is the case?</p> <p>5 A. No.</p> <p>6 Q. And so far as you're aware, has the</p> <p>7 Pottegard study been retracted?</p> <p>8 A. No.</p> <p>9 Q. Other than plaintiffs' counsel's</p> <p>10 hypothetical, do you know of any source for such a</p> <p>11 theory?</p> <p>12 A. No.</p> <p>13 Q. At the time the Pottegard study was</p> <p>14 conducted, do you know whether other API manufacturers</p> <p>15 had announced any discovery of an NDMA or NDEA impurity</p> <p>16 in their API being sold in Denmark?</p> <p>17 A. I don't know.</p> <p>18 Q. And you know that the Pottegard study</p> <p>19 looked at patients in Denmark; correct?</p> <p>20 A. Yes.</p> <p>21 Q. So at that time, was there any better data</p> <p>22 available to the authors of the Pottegard study about</p> <p>23 exposure to valsartan containing an impurity?</p> <p>24 A. No.</p>	<p style="text-align: right;">Page 397</p> <p>1 cancer finding in that study?</p> <p>2 A. Yes.</p> <p>3 Q. Do you remember a question about a</p> <p>4 sentence in your report that said there were not</p> <p>5 statistically significant associations with cancer</p> <p>6 overall or any specific answer?</p> <p>7 A. Yes.</p> <p>8 Q. And plaintiffs' counsel suggested that</p> <p>9 your report was inaccurate because it did not mention a</p> <p>10 liver cancer finding in that sentence; correct?</p> <p>11 A. That's what he said.</p> <p>12 MR. SLATER: Objection. You can answer.</p> <p>13 BY MR. INSOGNA:</p> <p>14 Q. Do you have your report in front of you?</p> <p>15 A. I do.</p> <p>16 Q. Look with me, if you would, at Page 39,</p> <p>17 where you discuss the Gomm study.</p> <p>18 A. Yes.</p> <p>19 Q. And if you would find that sentence with</p> <p>20 me where it says, "In other words, taking NDMA</p> <p>21 containing the valsartan impurity" -- you see that?</p> <p>22 A. Yes.</p> <p>23 Q. And that was the sentence that plaintiffs'</p> <p>24 counsel called to your attention; correct?</p>
<p style="text-align: right;">Page 396</p> <p>1 Q. So how, if at all, does plaintiffs'</p> <p>2 counsel's hypothetical about the Pottegard study impact</p> <p>3 your opinions of the Pottegard study?</p> <p>4 A. Not at all.</p> <p>5 Q. And I believe you were asked some</p> <p>6 questions about confounding in the Pottegard study;</p> <p>7 right?</p> <p>8 A. Yes.</p> <p>9 Q. And was it your testimony that there is</p> <p>10 residual confounding in the Pottegard study?</p> <p>11 A. Yes, I think that was one of the noted</p> <p>12 limitations.</p> <p>13 Q. And did the potential for residual</p> <p>14 confounding impact your opinions in any way in this</p> <p>15 case?</p> <p>16 A. No.</p> <p>17 Q. In the Pottegard study, was there any</p> <p>18 incidence of liver cancer in either the control or</p> <p>19 study arm of the subject?</p> <p>20 A. There was not.</p> <p>21 Q. Plaintiffs' counsel asked you some</p> <p>22 questions today about the Gomm study as well; right?</p> <p>23 A. Yes.</p> <p>24 Q. Specifically asked you about the liver</p>	<p style="text-align: right;">Page 398</p> <p>1 A. Yes.</p> <p>2 Q. Can you read to me the next sentence in</p> <p>3 your report?</p> <p>4 A. "The analysis of individual cancer types</p> <p>5 did show a slight statistically significant association</p> <p>6 but not causation between potentially NDMA's containing</p> <p>7 valsartan and liver cancer, with the adjusted hazard</p> <p>8 ratio, but not for any other cancer evaluated in the</p> <p>9 listed cancers there."</p> <p>10 Q. So the sentence immediately after the one</p> <p>11 that plaintiffs' counsel focused on discussed the liver</p> <p>12 cancer finding in the Gomm paper?</p> <p>13 A. Yes.</p> <p>14 MR. SLATER: Objection. You can answer.</p> <p>15 BY MR. INSOGNA:</p> <p>16 Q. In writing this the way that you did, were</p> <p>17 you attempting to conceal the liver cancer finding in</p> <p>18 any way?</p> <p>19 MR. SLATER: Objection. You can answer.</p> <p>20 A. Obviously not. It's almost like this</p> <p>21 first sentence should have continued and said other</p> <p>22 than the analysis of individual cancer types showing</p> <p>23 the association in liver -- that's probably what I</p> <p>24 meant and I made an error there and made it into two</p>

<p style="text-align: right;">Page 399</p> <p>1 different sentences.</p> <p>2 BY MR. INSOGNA:</p> <p>3 Q. Turn with me if you would to the</p> <p>4 discussion of the Hidajat paper, which you have on Page</p> <p>5 43 of your report.</p> <p>6 Plaintiffs' counsel asked you a number of</p> <p>7 questions about the Hidajat study today; right?</p> <p>8 A. Yes.</p> <p>9 Q. He asked you a series of questions about</p> <p>10 whether the study subjects stayed in the same job title</p> <p>11 versus in the same job department; right?</p> <p>12 A. Yes.</p> <p>13 Q. Do you have the Hidajat paper in front of</p> <p>14 you?</p> <p>15 A. Yes.</p> <p>16 Q. If you would look with me on Page 251 in</p> <p>17 the right-hand column under the heading exposure</p> <p>18 assessment. About three-quarters of the way through</p> <p>19 that paragraph --</p> <p>20 A. Yes.</p> <p>21 Q. -- there's a sentence that starts,</p> <p>22 "Lifetime cumulative exposures."</p> <p>23 Do you see that?</p> <p>24 A. Yes.</p>	<p style="text-align: right;">Page 401</p> <p>1 MR. SLATER: Got it. Thank you.</p> <p>2 BY MR. INSOGNA:</p> <p>3 Q. Can you read the sentence that begins,</p> <p>4 "Due to"?</p> <p>5 A. "Due to the complexity of exposure</p> <p>6 patterns and the numerous chemicals used in the rubber</p> <p>7 production process, disentangling exposure response</p> <p>8 associations between specific suspected carcinogens and</p> <p>9 cancer risk in this industry remains difficult."</p> <p>10 Q. And did that language inform your opinions</p> <p>11 about the Hidajat study?</p> <p>12 A. Well, it points out what I think I pointed</p> <p>13 out and other experts have pointed out, is that there's</p> <p>14 just so much confounding to isolate the contribution of</p> <p>15 a given toxin or a putative carcinogen is nearly</p> <p>16 impossible, and they're stating this in that sentence.</p> <p>17 Q. And in the Hidajat study they list the</p> <p>18 carcinogens to which workers are exposed; correct?</p> <p>19 A. Yes.</p> <p>20 Q. And if you look with me on Page 250 just</p> <p>21 above where you started reading the paragraph that</p> <p>22 starts, "Important carcinogenic exposures."</p> <p>23 Do you see that?</p> <p>24 A. Which paragraph?</p>
<p style="text-align: right;">Page 400</p> <p>1 Q. Can you read that sentence?</p> <p>2 A. "Lifetime cumulative exposures to rubber</p> <p>3 dust, rubber fumes, or N-nitrosamines were calculated</p> <p>4 for each worker based on the assumed number of years</p> <p>5 worked and department."</p> <p>6 Q. And as you read that sentence -- well,</p> <p>7 what does that sentence tell you about the way</p> <p>8 nitrosamine exposures were calculated in the study?</p> <p>9 A. They were calculated based on the</p> <p>10 department of which the worker worked in, and so</p> <p>11 allowing them with the same job title to move around to</p> <p>12 different jobs within that department wouldn't affect</p> <p>13 this analysis.</p> <p>14 Q. If you would turn back one page to 250 in</p> <p>15 Hidajat, please.</p> <p>16 A. 250?</p> <p>17 Q. Yes, the first page of the study. At the</p> <p>18 very end of that page, there's a sentence that begins,</p> <p>19 "Due to," and continues onto the next page.</p> <p>20 Do you see that?</p> <p>21 MR. SLATER: I'm sorry. I lost where you</p> <p>22 are. Could you just tell me again, Nick, please?</p> <p>23 MR. INSOGNA: Yeah, the very end of Page</p> <p>24 250 in Hidajat.</p>	<p style="text-align: right;">Page 402</p> <p>1 Q. The right-hand column, under the gray</p> <p>2 table there.</p> <p>3 A. What page?</p> <p>4 Q. On Page 250, the first page.</p> <p>5 A. Oh, the first page. I'm sorry. Okay.</p> <p>6 Okay. "Important." Yes.</p> <p>7 Q. "Important carcinogenic exposures."</p> <p>8 A. Uh-huh.</p> <p>9 Q. Do you see that list of carcinogens?</p> <p>10 A. Yes.</p> <p>11 "N-nitrosamines, rubber dust, rubber</p> <p>12 fumes, polycyclic aromatic hydrocarbons including</p> <p>13 phthalates, aromatic amines, and beta-naphthylamine,</p> <p>14 and solvents including benzene, among others."</p> <p>15 Q. And when you talk about the potential for</p> <p>16 confounding and the inability, I believe you read the</p> <p>17 sentence, to disentangle exposures, are those the other</p> <p>18 exposures that concerned you with the study?</p> <p>19 A. Yes.</p> <p>20 Q. Over the course of this deposition, you've</p> <p>21 been asked a few times about whether you'd like to see</p> <p>22 certain corporate documents and depositions.</p> <p>23 Do you recall those questions?</p> <p>24 A. Yes.</p>

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1 Q. And did you in the course of your review
2 look at any company documents?
3 A. Yes.
4 Q. I'd like to look at your reliance list, if
5 we could. And if we could pull that up on the screen.
6 A. Okay.
7 Q. I don't know which number this is in the
8 record.
9 MS. WITTLAKE: (Inaudible) report, which
10 is Exhibit 7. It starts on Page 90.
11 MR. INSOGNA: Okay. Thank you.
12 MR. SLATER: I had marked his most recent
13 list of materials considered as Exhibit 11, I think.
14 MR. INSOGNA: Why don't -- we can put up
15 11.
16 MR. SLATER: I'm just letting you know. I
17 thought you were asking. I didn't know if you were
18 asking me. Trying to be helpful.
19 A. Appreciate it.
20 MR. SLATER: Anytime. I'm trying to get
21 the last questioner done.
22 MR. INSOGNA: If you would go to Page 2 of
23 that document, Kate.
24 MR. SLATER: What page did you say? 18?

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1 MR. INSOGNA: Page 2 of the document.
2 MR. SLATER: Oh, Page 2.
3 BY MR. INSOGNA:
4 Q. Dr. Catenacci, do you have that in front
5 of you?
6 If you would turn with me also to Page 2.
7 A. Yes.
8 Q. You see there's a heading company
9 documents produced?
10 A. Yes.
11 Q. And that continues for a few pages. I
12 want to go through these documents.
13 But first question, did you review these
14 documents that were provided to you?
15 A. Yes.
16 Q. I see the first one listed there is a Teva
17 health hazard assessment re valsartan.
18 That was a document you had in your
19 possession?
20 A. Yes.
21 Q. And did you review it?
22 A. Yes.
23 Q. And there are another one, two, three, I
24 see, health hazard assessments there; correct?

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1 A. Yes.
2 Q. Did you review each of those documents in
3 preparing your opinions?
4 A. Yes.
5 Q. There's also a toxicological assessment of
6 NDMA impurity in valsartan by Dr. Nudelman?
7 A. Yes.
8 Q. Did you review that document?
9 A. Yes.
10 Q. And I believe plaintiffs' counsel asked
11 you yesterday if you reviewed the deposition of Dr.
12 Nudelman.
13 Do you recall that?
14 A. Yes.
15 Q. And did you review that deposition?
16 A. I reviewed it. It's been some time since
17 I last looked at it.
18 Q. And this next document here is a ZHP root
19 cause analysis.
20 Do you see that?
21 A. Yes.
22 Q. Is that a document you reviewed in
23 preparing your opinion?
24 A. Yes.

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1 Q. And below that is a Mylan root cause.
2 Do you see that?
3 A. Yes.
4 Q. Is that also a document you reviewed in
5 preparing your opinions?
6 A. Yes.
7 Q. And below that is a Teva risk assessment
8 before for valsartan Huahai.
9 Do you see that?
10 A. Yes.
11 Q. Is that a document you reviewed in
12 preparing your opinions?
13 A. Yes.
14 Q. And going over the next page, I see
15 another risk assessment and several more tox
16 assessments listed here, as well as some additional
17 data.
18 You see all these listed?
19 A. Yes.
20 Q. Are these all documents that you reviewed
21 in preparing your opinions in this case?
22 A. Yes.
23 MR. SLATER: Objection.
24 BY MR. INSOGNA:

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1 Q. Now, you --

2 THE REPORTER: I'm sorry. Sorry. Was the

3 answer yes?

4 A. Yes.

5 THE REPORTER: Thank you.

6 BY MR. INSOGNA:

7 Q. You did not cite these documents in the

8 body of your report, did you?

9 A. No.

10 Q. Did any of these documents influence or

11 alter your independent opinions in any way?

12 A. No.

13 Q. And I believe in response to plaintiffs'

14 counsel questions you testified that it would be

15 interesting to see all available evidence.

16 Was it necessary for you to review

17 corporate depositions in order to form your opinions in

18 this case?

19 A. No.

20 Q. Was it necessary for you to review

21 internal corporate documents like these tox assessments

22 that you did review in order to form your opinions in

23 this case?

24 A. No.

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1 Q. Why is that?

2 A. They weren't part of my analysis. They

3 were sort of background information, but they weren't

4 fundamental data points and studies that I relied upon

5 to answer the question that was being asked of me.

6 Q. In formulating a scientific opinion about

7 causation or whether there's elevated risk, would you

8 rely on what a company said about its own internal risk

9 assessments in formulating those opinions?

10 A. No.

11 Q. Would a company's internal risk assessment

12 or testimony dictate how you render causation opinions

13 in a case like this?

14 A. No, not at all.

15 Q. One of the things that plaintiffs' counsel

16 focused on in his questioning was the levels of

17 impurity in valsartan tablets.

18 Do you recall those questions?

19 A. Yes.

20 Q. When you -- first of all, in your report,

21 do you identify the levels of putative nitrosamine

22 impurities that you looked at in formulating your

23 opinion?

24 A. Yes. They're in the table that was from

Page 409

1 the FDA.

2 Q. And where did you take that -- you just

3 said you took that data from FDA?

4 A. Yes.

5 Q. And why is that the source that you chose

6 to use?

7 A. This is the publicly-available data that

8 was provided after an extensive analysis of multiple

9 lots and to look at the range and to evaluate that.

10 Q. And to the extent that there are other

11 potential data points on that question, would those

12 influence your opinions in any way?

13 A. No. I was looking to see what the levels

14 were, what their ranges were, but really to get a sense

15 of what might be a mean exposure level that a patient

16 might have in a given situation.

17 Q. Over the course of this two days of

18 deposition now, did any of plaintiffs' counsel's

19 hypotheticals or questions cause you to alter your

20 opinions in any way?

21 A. No.

22 MR. INSOGNA: Looking at notes here, Adam.

23 Give me one moment.

24 MR. SLATER: No. No notes.

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1 MR. INSOGNA: I'm smiling very widely. I

2 know you're always concerned about that.

3 Okay. I do not have any more questions

4 for Dr. Catenacci.

5 MR. KUM: So I do have some questions. So

6 Adam, here's some food for thought. We could argue

7 over this for --

8 MR. SLATER: I'm not going to --

9 MR. KUM: -- a couple minutes, but I only

10 have a couple of minutes, and we'd be done.

11 MR. SLATER: This is what I'll say. If

12 you're telling me a couple minutes, some people's

13 couple minutes is 20, some is two.

14 MR. KUM: No. No, I'm going to be less

15 than five minutes.

16 MR. SLATER: Okay. I just want to make it

17 really clear for the record I'm not going to create a

18 big blowup over five minutes of questions. I'm

19 assuming that, Bob, you're the only one who intends to

20 question, that it's not going to be a string of people.

21 So I'm making this concession because it's my

22 understanding only you have to question.

23 I am reserving all my rights. I'm

24 agreeing to this without prejudice to our position that

<p style="text-align: right;">Page 411</p> <p>1 multiple defense lawyers should not question a defense 2 expert. But if it's going to be less than five 3 minutes, I don't think it's worthwhile to create a big 4 battle over it at this point. 5 Hopefully it will go smoothly and we'll 6 move on, and I'm assuming it will. So -- but I'm 7 reserving all my rights. It's not a concession. I 8 wouldn't want to hear in a conference some day that I 9 agreed to it today and -- 10 MR. KUM: Understood. 11 MR. SLATER: -- that we waived our rights 12 or anything. I'm just doing it to try to be an 13 easygoing guy today. 14 MR. KUM: Absolutely cool. 15 John, are we back on the record? Let me 16 know if we ever went off the record. 17 THE REPORTER: No -- yeah, we actually 18 didn't go off the record. 19 MR. KUM: Okay. Well, that's perfect. 20 EXAMINATION 21 BY MR. KUM: 22 Q. Dr. Catenacci, this is Bob Kum. I just 23 have a few follow-ups. I'm going to share my screen 24 with you. Plaintiffs' counsel -- I think he marked</p>	<p style="text-align: right;">Page 413</p> <p>1 A. I agree with that. 2 Q. I'm going to scroll a little bit farther 3 down. It's on Page 461. 4 Do you see the header clinical evidence of 5 carcinogenesis due to contamination of medications? Do 6 you see that? 7 A. Yes. 8 Q. In the middle of it -- and I'll just 9 highlight it -- it reads, "A negative association was 10 reported for the incidence of colorectal cancer. Of 11 interest is the absence of mention of an association 12 with HCC, the primary tumor type that was found in 13 preclinical carcinogenicity in multiple species." 14 Did I read that correctly? 15 A. Yes. 16 Q. In layman's terms, what is that -- what is 17 the significance? What does that mean when they talk 18 about the absence of mention of an association of HCC, 19 and how does that relate to your opinions in this case? 20 A. Well, first, just to point out, HCC means 21 hepatocellular carcinoma, which is liver cancer. And 22 so they're noting that it's of interest that there's no 23 association or mention of this with HCC, which is what 24 preclinical models have suggested.</p>
<p style="text-align: right;">Page 412</p> <p>1 this I wrote down Exhibit 16. 2 MR. KUM: Is that correct, John? 3 THE REPORTER: I can double-check. One 4 moment. 5 MR. KUM: Well, whatever exhibit this is. 6 We'll just -- I want to -- 7 THE REPORTER: Yes, it is Exhibit 16. 8 BY MR. KUM: 9 Q. Doctor, can you see this study? 10 A. Yes. 11 Q. And you had indicated you had not seen 12 this prior to today; correct? 13 A. Yes. 14 Q. I want to read the first three sentences. 15 It says, "The causes of cancer are 16 manifold. About one quarter to one third of cancers, 17 depending on the specific tumor and population, are 18 caused by infectious agents, while a smaller fraction 19 can be attributed to genetic predisposition. A larger 20 number, perhaps 50 percent or more, arise from 21 environmental and behavioral causes, such as smoking, 22 alcohol, dietary factors, obesity, and pollution." 23 What's your reaction to that statement? 24 Do you agree or disagree with that?</p>	<p style="text-align: right;">Page 414</p> <p>1 So he's pointing it out that it hasn't 2 been demonstrated here in this study. 3 Q. On the first day, I believe plaintiffs' 4 counsel asked you the generic question of whether you 5 agreed NDMA and NDEA is classified as a probable 6 carcinogen. 7 Do you remember those questions? 8 A. Yes. 9 Q. And I don't believe he followed up with 10 asking you an explanation of what probable carcinogen 11 means as it relates to the IR classification. 12 Is that correct? 13 MR. SLATER: Objection. 14 A. Correct. 15 BY MR. KUM: 16 Q. Let me just pull up for you the IARC 17 classification. 18 So Doctor, you agree that IARC has, in 19 determining whether a chemical or substance is 20 carcinogenic, groups it into different categories; 21 correct? 22 A. Yes. 23 Q. And Group 1 here indicates, "The category 24 is used when there is sufficient evidence of</p>

<p style="text-align: right;">Page 415</p> <p>1 carcinogenicity in humans. In other words, there is 2 convincing evidence that the agent causes cancers in 3 humans." 4 Did I get that correct? 5 A. Yes, sufficient evidence of 6 carcinogenicity in humans. Yes. 7 Q. Is NDMA classified as a Group 1 8 carcinogen? 9 A. No. 10 Q. Is NDEA classified as a Group 1 11 carcinogen? 12 A. No. 13 Q. Is it correct that those two substances 14 I've mentioned are classified as Group 2A? 15 A. Yes. 16 Q. Let's go to the definition of what 2A is. 17 Do you see that, Doctor? 18 A. Yes. 19 Q. It says here that, "The category is used 20 when there is limited evidence of carcinogenicity in 21 humans and either sufficient evidence of 22 carcinogenicity in experimental animals or strong 23 mechanistic evidence showing that the agent exhibits 24 key characteristics of human carcinogens."</p>	<p style="text-align: right;">Page 417</p> <p>1 Did I get that correct? 2 MR. SLATER: Objection. You can answer. 3 A. Yes, I mentioned that yesterday. 4 BY MR. KUM: 5 Q. I want to go down here to what IARC says 6 about this. 7 Do you see there's the header that says, 8 "What does the classification mean in terms of risk?" 9 Do you see that? 10 A. Yes. 11 Q. And it says here that, "The classification 12 indicates the strength of evidence that a cause or 13 agent can cause cancer. The IARC monographs programme 14 seek to identify agents that are cancer hazards, 15 meaning they pose the potential for the exposure to 16 cause cancer. However, the classification does not 17 indicate the level of risk associated with a given 18 level or circumstance of exposure." 19 Is that what you meant yesterday when you 20 talked about IARC not classifying risks of a chemical? 21 MR. SLATER: Objection. You can answer. 22 A. That's exactly what I was referring to. 23 BY MR. KUM: 24 Q. Further on, do you see here the header</p>
<p style="text-align: right;">Page 416</p> <p>1 Did I read that correctly? 2 A. Yes. 3 Q. And does that comport with your 4 understanding of what a Group 2A carcinogen is? 5 A. Yes. 6 Q. It goes to say that, "Limited evidence of 7 carcinogenicity means that a positive association has 8 been observed between exposure to the agent and cancer, 9 but that other explanations for the observations, 10 technically termed chance, bias, or confounding, could 11 not be ruled out with reasonable confidence." 12 Did you read that -- did you see that, 13 Doctor? 14 A. Yes, I see that. 15 Q. And does that comport with your 16 understanding of why they only considered NDMA or NDEA 17 to have limited evidence of carcinogenicity? 18 MR. SLATER: Objection. You can answer. 19 A. Yes. 20 BY MR. KUM: 21 Q. Yesterday you also mentioned that -- I 22 believe if -- let me see if I've got my notes 23 correctly -- that IARC does not look at chemicals from 24 a risk perspective.</p>	<p style="text-align: right;">Page 418</p> <p>1 that says, "What is the difference between risk and 2 hazard?" 3 A. Yes. 4 Q. It says here, "The IARC monographs 5 programmes identifies cancer risks but not does 6 evaluate the risks associated with special levels or 7 circumstances of exposures." 8 It then goes on to state -- tell me if I'm 9 reading this correctly -- "The distinction between 10 hazard and risk is important. An agent is considered a 11 cancer hazard if it is capable of causing cancer under 12 some circumstances. Risk measures the probability it 13 will occur, taking into account the level of exposure 14 to the agent. The IARC monographs may identify cancer 15 hazards even when risks are very low with known 16 patterns of use or exposure," period. 17 Again, does that comport with your 18 testimony and the concept you were trying to convey 19 yesterday? 20 MR. SLATER: Objection. 21 A. Yes, that's exactly what I was referring 22 to. 23 MR. KUM: Counsel, thank you very much. I 24 appreciate your accommodation.</p>

<p style="text-align: right;">Page 419</p> <p>1 MR. SLATER: No problem. So I assume it's 2 my turn to go back now, based on our back-and-forth? I 3 wasn't saying that pejoratively. Since we -- I think 4 we've agreed no other defense counsel ask questions, 5 I'm going to pick up now.</p> <p>6 EXAMINATION</p> <p>7 BY MR. SLATER:</p> <p>8 Q. Did you -- let me just fix this. 9 Did you ask the defense if they had any 10 documents that could impact your opinions?</p> <p>11 A. I don't think so.</p> <p>12 Q. Counsel asked you if the defendants tried 13 to influence you or suggest opinions to you. 14 Without going into any detail, you've been 15 working with defense counsel for months since March and 16 working with them while you were writing your report 17 and preparing for your deposition; right?</p> <p>18 MR. INSOGNA: Object to form.</p> <p>19 A. I've been working with them, yes.</p> <p>20 BY MR. SLATER:</p> <p>21 Q. And you've had multiple meetings with them 22 long before you started preparing for the deposition 23 about what you were being asked to do, and they were 24 providing documents to you, and you said you were going</p>	<p style="text-align: right;">Page 421</p> <p>1 Q. Not all epidemiologic studies are equal, 2 right, in terms of their value and their limitations; 3 right?</p> <p>4 A. That's I think what I've been saying.</p> <p>5 Q. Some -- rephrase. 6 So when you say human epidemiologic 7 studies have a certain level of value or validity, 8 there are some that actually don't really have much 9 validity or usefulness at all, and there are some that 10 are very valid and useful?</p> <p>11 It depends on the specific study, the 12 limitations, and what was being addressed; right?</p> <p>13 MR. INSOGNA: Object to form.</p> <p>14 A. I think that's what I was relaying 15 throughout the deposition, is that there are different 16 levels of evidence and their weight should be different 17 depending on how strong the study is, how much weight 18 should we put towards it.</p> <p>19 BY MR. SLATER:</p> <p>20 Q. Do you have your report there?</p> <p>21 A. Yes.</p> <p>22 Q. Could you go to Page 39, please? 23 Counsel asked you about some of the 24 language and wording you used in your discussion of the</p>
<p style="text-align: right;">Page 420</p> <p>1 back and forth with them pretty regularly; right? 2 MR. INSOGNA: Object to form.</p> <p>3 A. We were discussing papers, usually what my 4 thoughts were about the paper and my opinion.</p> <p>5 BY MR. SLATER:</p> <p>6 Q. You were asked just by counsel a few 7 moments ago about the Pottgard study, and my 8 paraphrase of what I heard was, "Yes, there's problems 9 with the data, but there's no better data, so that's 10 what we have to work with, basically." 11 Right?</p> <p>12 MR. INSOGNA: Object to form.</p> <p>13 A. That's an interesting paraphrase. That's 14 not how I took that. It was more what we've been 15 discussing the whole time, which is all studies have 16 limitations, and there are different levels of evidence 17 that we put different weights on, and that cohort 18 studies like those, even epi data, are by far the 19 highest level of evidence that we have here, albeit 20 with known limitations that we talked about.</p> <p>21 BY MR. SLATER:</p> <p>22 Q. Well, epidemiologic studies is a category 23 of scientific data; right?</p> <p>24 A. Yes.</p>	<p style="text-align: right;">Page 422</p> <p>1 Gomm study. I'd like to go down to the bottom of the 2 paragraph about Gomm.</p> <p>3 The second-to-last paragraph, you say, 4 "With multiple testing that has been conducted between 5 the two studies, including for each of the various 6 cancers, there is potential that a positive finding 7 here in Gomm et al is due to mere chance, and further 8 analysis is warranted to derive firm conclusions." 9 Right?</p> <p>10 A. Right.</p> <p>11 Q. There's also the possibility or 12 potential -- rephrase.</p> <p>13 There's also the potential that the 14 positive finding in Gomm is not due to mere chance but 15 actually indicates a real causal association?</p> <p>16 That's possible also; right?</p> <p>17 MR. INSOGNA: Object to form.</p> <p>18 A. A real causal association? Now we're 19 going to -- that's a possibility. Anything's possible, 20 but it's less likely, given all the dataset that we're 21 looking at, and that's why I qualified that this is 22 something that would need to be followed up on in an 23 independent analysis to confirm these findings, 24 especially since other studies haven't shown a liver</p>

<p>Page 423</p> <p>1 finding, and we just looked at that one article from 2 Adamson, who notes himself it's interesting that 3 there's no association with HCC. 4 So I think the theme of the argument here 5 from my perspective is that there's no consistency. 6 Yes, there is this one data point, but there are others 7 that are in direct conflict with this, which makes it 8 less likely and more likely random until proven 9 otherwise. 10 BY MR. SLATER: 11 Q. You were asked about the company 12 documents -- 13 A. Yes. 14 Q. -- that are listed on your amended list 15 of materials considered? 16 A. Yes. 17 Q. You didn't mention any of them in your 18 report, with the exception of referencing the documents 19 that provided you information about the -- well, let me 20 withdraw that and ask it differently. 21 The documents are not -- rephrase. 22 Looking at the company documents produced 23 that counsel just asked you about, you don't discuss 24 those in your report; right?</p> <p>Page 424</p> <p>1 A. No. 2 Q. Meaning I'm correct; right? 3 A. Yes. 4 Q. A double negative conundrum. 5 There was nothing in those doc -- well, 6 rephrase. 7 Yesterday when I asked you about doctor -- 8 rephrase. 9 Yesterday when I asked you about Raphael 10 Nudelman's deposition, if my recollection is correct, 11 you didn't even know who Raphael Nudelman was 12 yesterday; right? 13 A. I had forgotten who he was and what that 14 one was about, because I hadn't read that one in some 15 time, like four months ago. I had read it, but it 16 clearly didn't play a role in my opinion, if that's the 17 question. 18 Q. The company documents -- well, let me ask 19 you this. 20 In Raphael Nudelman's deposition, there's 21 nothing that you cited to from that deposition in your 22 report; right? 23 A. Not specifically. 24 Q. Do you recall what he said in his</p>	<p>Page 425</p> <p>1 deposition at all? 2 A. I'd have to go back and look at the 3 details. 4 Q. Do you know who he works for? 5 A. I know now after reviewing just briefly 6 what it was, was that it was the toxicologist that was 7 evaluating on the side of the defense -- I think Teva. 8 Q. You just -- you reviewed that today to 9 recollect? 10 A. I just know that that's what it was. I 11 haven't reviewed the whole deposition since yesterday, 12 no. 13 Q. Can you tell me anything he said in the 14 deposition at all? 15 A. I didn't memorize it, no. 16 Q. Can you tell me anything at all about the 17 deposition? Do you remember anything he said? 18 MR. INSOGNA: Object to form. 19 A. I'm happy to look at it and tell you what 20 I thought about it. 21 BY MR. SLATER: 22 Q. You don't remember anything from the 23 deposition as you sit here now; right? 24 A. I'm -- it's been a long time since I</p> <p>Page 426</p> <p>1 looked at it. 2 Q. So I'm correct? 3 A. That I can't -- 4 Q. You don't recall anything about the 5 deposition as you sit here now; correct? 6 A. Other than it was a toxicological 7 analysis, that's all I -- no, I don't know the details. 8 I didn't memorize numbers or anything like that. 9 Q. Go to the company documents produced list 10 that you were asked about. Let's look at the first 11 document, the July 6th, 2018, Teva health hazard 12 assessment regarding valsartan. 13 What did that assessment conclude; do you 14 recall? 15 MR. INSOGNA: Object to form. 16 A. My recollection of these are they're sort 17 of similar to the Fairs (ph) data, in the sense that 18 they're just sort of reporting all adverse events in 19 patients taking the medications by a monthly sort of 20 documentation to follow, if I recall. 21 BY MR. SLATER: 22 Q. When did you last look at that document? 23 A. Oh, it would have been several months ago. 24 Q. If you had seen anything in any of these</p>
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<p>Page 427</p> <p>1 company documents that was of any significance to you, 2 is it fair to assume you would have discussed that in 3 your report? 4 A. No. That was not something that I was 5 relying on from an objective standpoint to answer the 6 question that I was asked. 7 Q. You said just a few minutes ago that it 8 was not necessary for you to see any of the corporate 9 depositions or documents that you weren't shown; but in 10 reality you don't know what's in those documents, so 11 you don't know whether you would want to see them or 12 not, because you don't know what's there; right? 13 MR. INSOGNA: Object to form. 14 A. We went through those questions, and I 15 don't know what's in there, so I can't say one way or 16 another. But if -- but I think what we're talking 17 about now you're asking about these other documents I 18 did see -- they didn't really play a role in what I was 19 doing here. 20 BY MR. SLATER: 21 Q. What I'm asking is this. 22 In terms of documents that were not 23 provided to you, there's no way for you to know whether 24 they would have been significant to you or not, because</p> <p>Page 428</p> <p>1 you haven't seen them; right? 2 A. That's fair to say. I don't know what's 3 in them. How can I tell you what I would do? 4 Q. You were asked about looking at the FDA 5 information regarding the levels of NDMA and NDEA in 6 the pills a few minutes ago; right? 7 A. Yes. 8 Q. If in reality the FDA information that you 9 accessed was incomplete in terms of the levels of NDMA 10 and NDEA, and that the levels were actually higher, and 11 the defendants produced to us documents showing higher 12 levels of those substances, you would have wanted to 13 know that so that you could have had the accurate 14 information to rely on and put in your report; right? 15 MR. INSOGNA: Object to form. Incomplete 16 hypothetical. 17 A. It would be important to know all data 18 points, as we've established. 19 BY MR. SLATER: 20 Q. If I could, I'd like to go to that 21 Oncologist -- you don't have a hard copy of it, right, 22 that editorial from The Oncologist? I think we have to 23 put it up on the screen. 24 MR. SLATER: Chris, do you think you could</p>	<p>Page 429</p> <p>1 put that up? I think it's Exhibit 16. And you can go 2 to Page 461, the area that the questioning was on just 3 a few minutes ago. That's great. Thank you. 4 BY MR. SLATER: 5 Q. Looking at Page 461 in the right-hand 6 column, you were asked a question about a study that is 7 discussed regarding ranitidine. 8 Do you see that? 9 A. Yes. 10 Q. Have you read that study? 11 A. I'm not sure what study they're referring 12 to here. All I can see is a number. This is a 13 commentary -- this paper. 14 Q. It's a study performed at Sloan Kettering 15 regarding ranitidine. 16 Did you see that study? 17 A. I don't know. I'd need to see the details 18 of what even the name of the paper is before I could 19 comment. 20 Q. You were -- rephrase. 21 Counsel read to you the statement that it 22 was of interest that there was no association mentioned 23 with liver cancer; right? 24 A. Yes.</p> <p>Page 430</p> <p>1 Q. Gomm did find a statistically significant 2 association to liver cancer; correct? 3 A. We talked about that, yes. 4 Q. You were shown by counsel some language 5 from the IARC document. 6 MR. SLATER: You could take that down, 7 Chris. Thanks. 8 BY MR. SLATER: 9 Q. You were asked some questions about an 10 IARC document by defense counsel, and it was suggested 11 that IARC did not consider the risk for Group 2A 12 carcinogens, if I understood correctly. 13 Did I understand correctly the question 14 you were asked? 15 MR. KUM: Object to form. Misstates 16 testimony. 17 BY MR. SLATER: 18 Q. Well, let me ask the question differently. 19 Do you recall that IARC said that NDMA -- 20 and I'm paraphrasing -- should be considered to be 21 carcinogenic to humans, for all practical purposes? 22 And the "for all practical purposes" I'm 23 quoting. I know that language was put out by IARC. 24 Are you familiar that I -- with IARC</p>
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1 saying that?

2 A. I don't remember seeing that just now, if

3 that's the question with what we were --

4 Q. No, I don't believe counsel showed that to

5 you just now.

6 So what I'm asking is, are you aware that

7 IARC with regard to NDMA said that it should be

8 considered carcinogenic to humans, quote, for all

9 practical purposes, close quote?

10 Are you aware that IARC said that?

11 THE WITNESS: I'm not aware -- I'm aware

12 of its listing as a 2A carcinogen.

13 MR. SLATER: I have no other questions.

14 MR. INSOGNA: I don't have any further --

15 MR. SLATER: We can get you to your

16 meeting, Doctor. It's time.

17 MR. INSOGNA: Thank you.

18 THE VIDEOGRAPHER: We are going off the

19 record at 4:02 PM.

20

21 [SIGNATURE RESERVED.]

22

23

24

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1 C E R T I F I C A T E

2

3 I, JOHN ARNDT, a Certified Shorthand

4 Reporter and Certified Court Reporter, do hereby

5 certify that prior to the commencement of the

6 examination, DANIEL CATENACCI, M.D., was sworn by me

7 via videoconference to testify the truth, the whole

8 truth and nothing but the truth.

9 I DO FURTHER CERTIFY that the foregoing is a

10 true and accurate transcript of the proceedings as

11 taken stenographically by and before me at the time,

12 place and on the date hereinbefore set forth.

13 I DO FURTHER CERTIFY that I am neither a

14 relative nor employee nor attorney nor counsel of any

15 of the parties to this action, and that I am neither a

16 relative nor employee of such attorney or counsel, and

17 that I am not financially interested in this action.

18

19

20

21 JOHN ARNDT, CSR, CCR, RDR, CRR

22 CSR No. 084-004605

23 CCR No. 1186

24

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1

2

3 I, DANIEL CATENACCI, M.D., the witness

4 herein, having read the foregoing testimony of the

5 pages of this deposition, do hereby certify it to be a

6 true and correct transcript, subject to the

7 corrections, if any, shown on the attached page.

8

9

10

11

12 DANIEL CATENACCI, M.D.

13

14

15 Sworn and subscribed to before me,

16 This _____ day of _____, 202_.

17

18

19 _____

20 Notary Public

21

22

23

24

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1

2 DEPOSITION ERRATA SHEET

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23 SIGNATURE:_____DATE:_____

24 DANIEL CATENACCI, M.D.

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Exhibit D

The Finding of N-Nitrosodimethylamine in Common Medicines

RICHARD H. ADAMSON,^{a,*} BRUCE A. CHABNER^{b,**}

^aTPN Associates, LLC, Germantown, Maryland, USA; ^bMassachusetts General Hospital Cancer Center, Harvard Medical School, Boston, Massachusetts, USA

*Former Director, Division of Cancer Etiology, National Cancer Institute

**Former Director, Division of Cancer Treatment, National Cancer Institute

The causes of cancer are manifold. About one quarter to one third of cancers, depending on the specific tumor and population, are caused by infectious agents, while a smaller fraction can be attributed to genetic predisposition. A larger number (perhaps 50% or more) arise from environmental and behavioral causes, such as smoking, alcohol, dietary factors, obesity, and pollution. In modern society, where innovation through chemistry leads to exposure to a broad range of new chemicals and drugs, chemical carcinogenesis is a concern. Recent announcements of withdrawal of the commonly used medications, ranitidine and valsartan, from the market due to contamination with the carcinogen N-nitrosodimethylamine (NDMA) have raised questions about the safety of these pharmaceuticals. This commentary will review the sources and properties of NDMA, assess the dangers it poses as a contaminant in foods and medicines, and suggest measures to mitigate contamination by such products.

NITROSOAMINES AS CARCINOGENS

The alert about NDMA contamination arose from the discovery of this carcinogen in several members of the sartan class of antihypertensives and similar findings of NDMA in ranitidine and related acid pump inhibitors. NDMA and other nitrosoamines are found ubiquitously in outdoor air, water, and soil in minor amounts. They are formed by the chemical interaction of a substituted (secondary or tertiary) amine and an oxidizing agent, usually a nitrite. Their chemical structure and the relevant reaction sequence are shown in Figure 1. In foods, the nitrosating agent responsible for forming NDMA is usually nitrous anhydride, which arises from a nitrite in acidic aqueous solution, as in the stomach [1]. Beer, cured meats such as bacon or sausage, and even water contain nitrosoamines in small amounts. Tobacco (either smoke or smokeless) contains nitrosoamines [2, 3]. Many different nitrosoamines have been evaluated for carcinogenic activity, with positive findings in many animal

species, as they induce tumors in the liver, kidney, and respiratory tract [4, 5]. Three nitrosoamines cause hepatocellular carcinoma (HCC) and other solid tumors in non-human primates. NDMA, the specific contaminant discovered in the medications, produced cancer in a number of experimental animal species and caused cirrhosis and hyperplastic nodules in monkeys, but not hepatocellular cancer [5–7]. On the basis of this evidence, nitrosoamines, including NDMA, have been classified as probable carcinogens in humans [8].

The mechanism of nitrosoamine carcinogenicity appears to be through its metabolic activation and covalent interaction with DNA, causing promutagenic DNA adducts. Structural and functional integrity can be restored to damaged DNA by various DNA repair processes, but if these fail or are overwhelmed by high exposures and adducts persist through a cycle of DNA replication, point mutations at critical sites in DNA may result.

THE PRESENCE OF NDMA IN MEDICATIONS

Estimates suggest that the average intake of the volatile nitrosoamines (including NDMA) from food sources is about 1 microgram per day. The Food and Drug Administration has identified 96 nanograms per day as the upper limit of safe daily ingestion from medicines.

Recent discoveries of NDMA in sartans and ranitidine have raised concerns of a potential risk for people taking these common medications. In 2018, the European Medicines Agency (EMA) called attention to valsartan contaminated by NDMA, as manufactured by Zhejiang Huahai Pharmaceuticals in China, leading to a recall of this medication in European Union (EU) countries [9]. In 2018, the FDA announced a voluntary recall of several valsartan products, manufactured by Zhejiang Huahai Pharmaceutical Co. Ltd. in China, and the same product made by Mylan Pharmaceuticals in India [10, 11]. Other sartans (candesartan, irbesartan, losartan, and olmesartan [12]) were found to contain, or were likely to

Correspondence: Bruce A. Chabner, M.D., Massachusetts General Hospital Cancer Center, Boston, Massachusetts, USA. E-mail: bruce.chabner@theoncologist.com; or Richard H. Adamson, Ph.D., TPN Associates LLC, 13625 Esworthy Road, Germantown, Maryland 20874, USA. E-mail: radamson.tpn@gmail.com Received February 21, 2020; accepted for publication April 1, 2020; published Online First on April 17, 2020. <http://dx.doi.org/10.1634/theoncologist.2020-0142>

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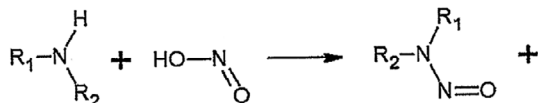


Figure 1. The formation of nitrosoamines. For NDMA R_1 and R_2 are methyl groups.

contain, nitrosoamines, as the sartans all possess a tetrazole ring formed chemically through a nitrite reaction with amines. While manufacturing processes and products are evaluated by the FDA before the final products are accepted for marketing, it is noteworthy that approximately 40% of finished medications in the U.S. are manufactured in overseas facilities, and approximately 80% of ingredients in medications finished in the U.S. come from abroad, principally from China and India, where FDA oversight of quality controls is challenging. The nitrosoamine contaminants in sartans likely arose as a result of a change in the manufacturing process in recent years [12], although formation of the toxic product could also result from contamination during any stage of drug production or use.

Of additional concern, in 2019, the Valisure pharmacy reported that ranitidine (the over-the-counter brand Zantac) and a related product, nizatidine, both used to counter gastric hyperacidity and reflux, contained unacceptable amounts of NDMA [13, 14]. Their report suggested that spontaneous breakdown of the ranitidine molecule could yield dimethylamine and nitrites, leading to NDMA formation. The amounts of NDMA in ranitidine, as tested by the FDA, if ingested as prescribed on a daily basis, would exceed the 96 nanogram daily limit by as much as ninefold, 860 nanograms [15].

THE RISK OF NDMA CARCINOGENESIS

It is difficult to calculate a specific cancer risk related to taking valsartan at the levels of contamination found. The generally acceptable risk for potential carcinogens in pharmaceuticals is one case of cancer per 100,000 subjects. The estimated risk calculated for valsartan ranges from 12 to almost 30 cases per 100,000 subjects, based on the European Medicines Agency assessment for an individual taking 320 mg valsartan, containing 24.1 micrograms NDMA and 3.7 micrograms NDEA per day for 4 years [12]. These estimates depend on an accurate accounting of the level of contamination in the available medication over time and the duration of exposure. The risk from NDMA in ranitidine and in its over-the-counter version, Zantac, is more problematic and may be greater. In use since 1981, it is the 50th most prescribed medication (>15 million prescriptions annually, plus over-the-counter use). The amount of NDMA found in ranitidine by the FDA, while lower than that found by the Valisure pharmacy, still exceeds the allowable daily limit (96 nanograms) by ninefold [15]. The actual amount of NDMA ingested by subjects taking ranitidine is still in question, although NDMA excreted in a 24-hour urine collection test of volunteers taking ranitidine increased 400-fold compared with baseline measurements [16]. An additional factor is the amount of nitrosoamine generated during storage of drug or nitrosoamine formed in gastric fluid, once the drug is internalized and contacts nitrite-containing foods, e.g., processed meats or nitrate-containing vegetables

such as lettuce, spinach, celery, or beets. Once ingested, nitrates can be converted to nitrites in the mouth or stomach. Thus, the total exposure of people taking ranitidine or nizatidine is not known at this time and may be subject to multiple factors, such as diet and gastric acidity, as well as impurities in the manufactured product and its storage.

CLINICAL EVIDENCE OF CARCINOGENESIS DUE TO CONTAMINATION OF MEDICATIONS

There is only limited clinical evidence at present suggesting that NDMA actually causes cancer in subjects taking sartans or ranitidine. A survey of 24,000 patients at Memorial Sloan Kettering Cancer Center compared subjects who reported ranitidine use at the time of diagnosis versus those who used other H-2 blockers or proton pump blockers. Ranitidine use was associated with a significant increase in the odds of presenting with breast, testicular, thyroid, and kidney cancer [17]. A negative association was reported for the incidence of colorectal cancer. Of interest is the absence of mention of an association with HCC, the primary tumor type that was found in preclinical carcinogenicity in multiple species. Although the specific organ targeted by a carcinogen may not be congruent across species, including human populations, HCC is an important potential target based on the frequency of this cancer in preclinical NDMA experiments. Definitive epidemiological studies of the association of these medicines with specific cancers in human clearly need to be performed.

Aside from their role as complete carcinogens, the nitrosoamines are likely to be co-factors or promoters in patients with underlying hepatic damage due to alcoholism, hepatitis, or hepatic steatosis. It is notable that the incidence of HCC had been steadily rising in the U.S. in the years from 2000 to 2013, although it has more recently plateaued and then declined with the introduction of antiviral therapy for hepatitis C virus [18].

Are there potential preventative agents or antidotes to nitrosoamine formation or induced DNA damage? Reducing agents such as sodium ascorbate (vitamin C) or sodium erythorbate might prevent or diminish damage in patients taking the drugs in question. Current formulations of ranitidine, including the ranitidine syrup taken by children, do not contain a reducing agent [19, 20].

In conclusion, NDMA contamination poses a potential carcinogenic risk of undetermined effect at present for those taking ranitidine, valsartan, or related medications on a regular basis. It is thus incumbent upon industry and the FDA to take steps to identify and eliminate the sources of contamination of medications with this class of carcinogen. At the same time, pharmaco-epidemiology studies should be performed to establish if there is excess risk in patients taking these medications.

DISCLOSURES

Bruce Chabner: PharmaMar, EMD Serono, Cyteir (C/A, H), Biomarin, Seattle Genetics, PharmaMar, Loxo, Blueprint, Immunomedics, Constellation (OI), Eli Lilly & Co., Genentech (ET). **Richard H. Adamson** indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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Editor's Note

On April 1, 2020, the U.S. Food and Drug Administration ordered the withdrawal of all ranitidine (Zantac) products from the commercial market and advised consumers to dispose of any of the product in their possession. This action was based on the finding of increased and unacceptable levels of NDMA in ranitidine stores at high temperature.

Exhibits E & F

Teva has designated Exhibit E as confidential, and ZHP has designated information in Exhibit F as confidential. Plaintiffs hereby challenge these designations. In accordance with the Court's Confidentiality and Protective order, Plaintiffs will forward the Exhibits to the Court directly via email for its in camera review.

Exhibit G

Risk of Cancer with Exposure to NDMA: An Analysis of Epidemiologic Data

By: Dr. Mahyar Etminan PharmD, MSc (Epidemiology)

A handwritten signature in black ink, appearing to read 'Mahyar Etminan', with a stylized flourish at the end.

July 6th, 2021

EXPERT REPORT OF Dr. Mahyar Etminan PharmD, MSc (Epidemiology)**Date of Report:** July 4th, 2021

Section 1. Qualifications

Section 2. What are NDMA or NDEA?

Section 3. NDMA or NDEA and carcinogenicity

Section 4. Valsartan containing NDMA or NDEA and carcinogenicity

Section 5. An epidemiologic assessment of the risk of cancer with NDMA or NDEA

Section 6. Objective of epidemiologic studies

Section 7. Study design and statistical concepts used to assess causation in epidemiology

Section 8. Epidemiologic studies of NDMA or NDEA and cancer: Methodology

Section 9. Epidemiologic studies of NDMA or NDEA and cancer: Results

Section 10. Evidence of specific types of cancer with NDMA/NDEA

Section 11. Assessing the causal relation between NDMA and different types of cancer using the Bradford Hill Criteria

Section 12. Summary

Section 13. Addendum

Section 14. References

the specific criteria carries a higher weight than others with regard to establishing a causal link. Rather, his intent was to show whether the totality of the evidence from the 9 criteria collectively suggest a causal link between a specific exposure with respect to an outcome (Bradford Hill) (Table 2).

I. Temporal Relationship: Temporality is a critical criterion to establish cause and effect. Temporality means that the cause (NDMA exposure in valsartan) precedes the outcome (cancer). In all the studies that assessed the effect of NDMA (dietary or occupational) the effect of NDMA on the 9 different types of aforementioned cancers, NDMA exposure was measured prior to the diagnosis or death due these different cancers. The study by *Hidajat*²⁵ excluded cancers that occurred early in the study to ensure that, due to the potential long-latency of the disease, the cancers ascertained in the study were caused by exposure to high levels of NDMA (NDMA in valsartan came before the incidence of the cancers). **Thus, this criterion plays a significant role in the presence of a causal link between NDMA/NDEA in valsartan and cancer.**

II. Biologic Plausibility: This criterion examines whether a biologically plausible mechanism for NDMA in valsartan to cause cancer exists. The answer is yes. Multiple regulatory agencies including the IARC has classified NDMA as carcinogenic. This classification has been granted in part due to an abundance of published animal studies that have shown that through a mechanism of genotoxicity, nitrosamines such as NDMA¹⁷ and NDEA¹⁸ can cause different cancers in animals including gastrointestinal cancers such as liver, esophageal^{14,16} pancreatic⁵⁷, colon⁵⁶, bladder cancer^{61,62}, prostate cancer⁶³, lung cancer⁵⁶ and blood cancer¹⁴. A number of animal studies have shown that NDMA and NDEA can cause a number of different types of cancer mainly through their genotoxic effects. **Thus, this criterion plays a significant role in the presence of a causal link between NDMA/NDEA in valsartan and cancer.**

III. Analogy: Analogy asks the question as to whether other carcinogens that are similar in chemical structure to NDMA in valsartan can also cause cancer. The answer is yes. Nitrites, which are compounds chemically similar to NDMA considered precursors to NDMA, have also shown to increase the risk of cancer⁶⁶. **Thus, this criterion plays a significant role in the presence of a causal link between NDMA/NDEA in valsartan and cancer.**

IV. Presence of a dose response relation: Presence of a dose-response relation also strengthens the causal argument. Usually, a causal link between a drug or any carcinogen is strengthened by a dose-response relation where a higher dose leads to a higher risk of an outcome, in this case, cancer. The study by *Hidajat*²⁵ has shown a dose response relation with all the 9 cancers deaths (**esophageal, stomach, colon, liver, pancreas, lung, bladder, prostate, blood**) and was the study with the longest follow up, large sample size and appropriate adjustment for important biases such as death due to competing events. Moreover, dietary epidemiologic studies on stomach cancer^{35,38,46,52}, pancreatic cancer³⁷ head and neck cancers^{46,42} colon cancer^{36,45}, lung cancer^{40,44} and blood cancers⁴¹ have also shown a positive dose response relation. The dietary study by *Jakszyn*⁴⁹ for prostate cancer and bladder cancer found an increase in the risk of both cancers with higher doses of NDMA, but the results did not reach statistical significance potentially due to small number of events. Data from large epidemiologic studies that specifically examined the effect of prolonged NDMA exposure through diet are not available for liver cancer. **Overall, presence of a dose response mainly driven by *Hidajat*²⁵ but also present in dietary epidemiologic studies**

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Exhibit H

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

**IN RE VALSARTAN, LOSARTAN,
AND IRBESARTAN PRODUCTS
LIABILITY LITIGATION**


THIS DOCUMENT RELATES TO ALL CASES

MDL NO. 2875

Civil NO. 19-02875 (RBK/JS)

**RULE 26 EXPERT REPORT OF
DIPAK PANIGRAHY, MD**

Date: July 6, 2021



Dipak Panigrahy, M.D.

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These 10 key characteristics of human carcinogens provide the basis for an objective approach to identify and categorize scientific findings relevant to cancer mechanisms when assessing whether a chemical is a potential human carcinogen^{24,25}. This systematic approach will assist future IARC working groups and other agencies in evaluating chemicals and pharmaceutical agents as potential human carcinogens, especially in the absence of convincing epidemiological data on many human cancers²⁴.

The key characteristics of carcinogens described by Smith et al. (2016)^{24,25} which are utilized by IARC are as follows:

10 Key Characteristics of Carcinogens

1. Can the agent act as an electrophile or be metabolically activated to an electrophile?
2. Is the agent genotoxic?
3. Does the agent alter DNA repair or cause genomic instability?
4. Does the agent induce epigenetic alterations?
5. Does the agent induce oxidative stress?
6. Does the agent induce chronic inflammation?
7. Is the agent immunosuppressive?
8. Does the agent modulate receptor-mediated effects?
9. Does the agent cause immortalization?
10. Does the agent alter cell proliferation, cell death, or nutrient supply?

The first four characteristics focus on the genotoxic nature of the chemical agent. The last six characteristics focus on the nongenotoxic mechanisms in the tumor microenvironment. These 10 key characteristics of human carcinogens are a roadmap for identifying and categorizing

scientific findings relevant to cancer mechanisms when asking whether a chemical or agent is a potential human carcinogen²⁴. The 10 key characteristics help in the identification of carcinogens as a first step in cancer prevention to prevent human suffering and death from cancer²⁵. I used these key characteristics to determine the biological plausibility of the mechanisms of action for both NDMA- and NDEA-induced carcinogenesis. The range of evidence available to determine whether NDMA exhibits these 10 key characteristics includes the following: animal cancer bioassays, studies of specific biological mechanisms in tissues and cells derived from humans, studies of specific biological mechanisms in tissues and cells derived from animals, and studies from exposures to humans. Starting in 1956, scientific studies show that NDMA has been extensively characterized as a presumed human carcinogen for decades. There is little available data from human exposures aside from incidental exposures because of occupation or diet, and unfortunate incidents of intentional poisoning. My analysis as to whether NDMA has each of these key characteristics is below.

NDMA EXHIBITS 9 OUT OF THE 10 KEY CHARACTERISTICS OF
CARCINOGENS

Most human carcinogens exhibit more than 1 of the 10 key characteristics with known carcinogens having an average of 3 to 4 key characteristics (e.g., benzene and polychlorinated biphenyls (PCBs)²⁴. By stunning contrast, NDMA exhibits 9 out of the 10 key characteristics which makes NDMA an extremely potent carcinogen with multiple mechanisms of action for its activity as a human carcinogen. My analysis below determined whether NDMA exhibits each of these key characteristics of carcinogens.

9 Key characteristics of NDMA

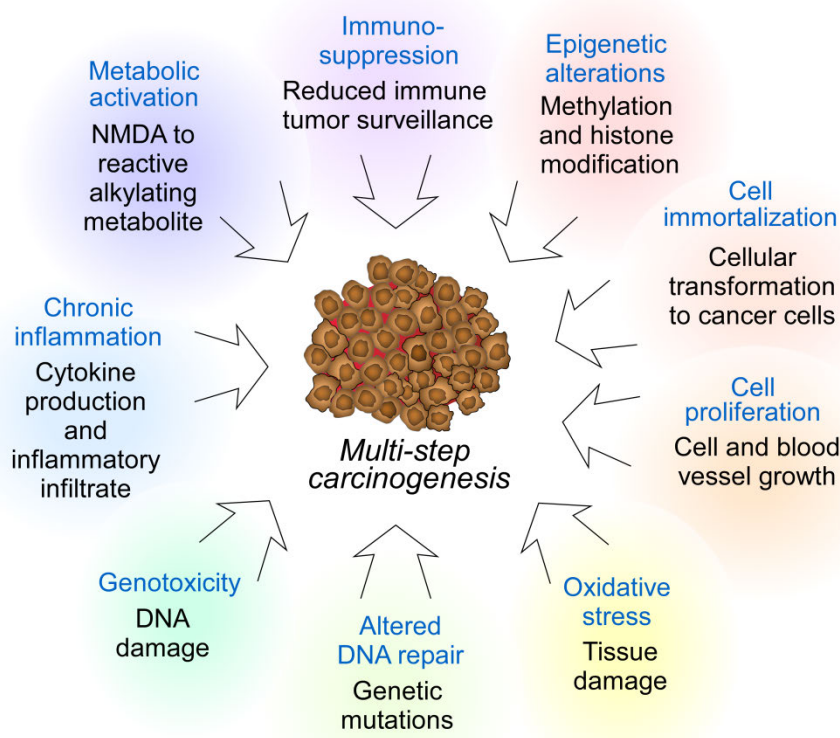


Figure 2. NDMA exhibits 9 of the 10 key characteristics of carcinogens.

Key Characteristic #1: NDMA is Metabolically Activated to Electrophiles Inducing the Formation of DNA Adducts

General Description

Many carcinogens do not directly cause cancer as the “parent molecule” but instead must first undergo a transformation process called metabolic activation to induce cancer. *Metabolic activation* is defined as the chemical conversion of a relatively benign (“harmless”) substance into a more hazardous (“cancer causing”) substance by biochemical processes in the cells and tissues. It is now well established with many thorough scientific studies that the cancer causing activity of

NDMA results from its metabolic transformation within susceptible tissues in the body to a chemically reactive agent which methylates a variety of molecules such as DNA forming DNA adducts¹⁰². Methylation is a chemical reaction in which a methyl group replaces a hydrogen atom.

Thus, before NDMA can cause cancer, the initial NDMA molecule that is ingested via a contaminated tablet or absorbed must undergo bioactivation to electron-seeking molecules (called electrophiles) that bind to DNA to form addition products, referred to as adducts, which lead to DNA damage and mutations. DNA adducts are segments of DNA bound to a cancer-causing chemical. The formation of DNA adducts is a key process that initiates the transition to a cancerous cell from a normal cell (carcinogenesis). The ability to form DNA and protein adducts is a common property of electrophilic and metabolically activated human carcinogens. For example, the classic mechanism of smoking includes metabolic activation of tobacco smoke to DNA adducts¹⁰³. The measurement of DNA adducts is one of the most common methods of assessing electrophilic activity both *in vitro* (outside the body) and *in vivo* (inside the body) to determine if this key characteristic occurs. The DNA adduct O6-alkylguanine has been shown to alter the DNA resulting in a mutation. The ability of carcinogens to form DNA adducts can lead to cancer¹⁰².

Why is metabolic activation important to the mechanism of carcinogenesis?

While some chemical carcinogens can directly cause cancer, many other carcinogens must undergo biotransformation by enzymes via metabolic activation before the chemical can cause cancer¹⁰⁴. Metabolism to an active metabolite is required for NDMA-induced cancer as the carcinogenic effects of NDMA are due to a metabolite rather than the compound itself. Metabolic activation of NDMA is required for its genotoxic and cancer causing activity. Several human enzymes can bio transform relatively inert chemical compounds to potent toxic and carcinogenic metabolites or reactive intermediates. These enzymes include cytochrome P450s (CYPs)¹⁰³. CYPs

are a superfamily of enzymes that catalyze chemical reactions of a wide variety of compounds, including drugs, carcinogens, and other chemicals. Many CYPs also activate carcinogens to electrophilic (electron loving), highly reactive compounds that bind to DNA which initiates the process of cancer formation¹⁰⁵.

Electrophiles and their nucleophilic targets can be described by their strength, which can predict how strong a reaction they undergo to cause cancer²⁵. Electrophiles are very dangerous since they have electron withdrawing groups capable of binding to N and O sites in the DNA which generates DNA adducts leading to cancer²⁵. Thus, any tissue or cell in the human body that expresses the enzyme (e.g., CYP) can metabolically activate the carcinogen. The cytochrome P450 enzymes that induce the metabolic activation of NDMA are present in many human tissues and cells including blood, liver, small and large intestine, bladder, lung, kidney, prostate, and pancreas¹⁰⁶.

NDMA induces metabolic activation in animal tissues and cells

Extensive studies in animal carcinogenesis bioassays, animal tissues and cells demonstrate that NDMA can cause cancer via metabolic activation inducing DNA adducts. NDMA is an alkylating agent that causes cancer via molecules called electrophiles. The electrophiles generated by NDMA induce DNA adducts⁶³. NDMA is capable of methylating many cell types to generate DNA adducts to initiate cancer throughout the body. In a high profile scientific paper in the high impact journal *Nature*, NDMA was elegantly demonstrated to cause persistent levels of DNA adducts (e.g. 6-methylguanine) in the rat liver and kidney DNA, which lead to cancer¹⁰². Liver microsomes from NDMA-treated rats also show an increased ability to convert NDMA to mutagenic molecules that can cause cancer.

While NDMA-induced DNA adduct formation occurs at a number of DNA sites, certain sites are preferred. The principal DNA adduct formed following exposure to NDMA is *N*7-methylguanine (representing about 65% of all adducts formed initially upon exposure); *O*6-methylguanine (O6-meG) is a secondary adduct (representing about 7% of all adducts formed initially upon exposure). Thus, NDMA methylates the DNA at certain sites to cause cancer in many tissues remote from the site of administration¹⁰⁷. NDMA at low doses (e.g., 0.2 to 2.6 ppm) in the drinking water of rats can induce DNA adducts (e.g., O6-meG) in the blood leukocytes (white blood cells) and liver leading to cancer formation^{63,108}. NDMA-induced DNA adducts accumulate rapidly in the blood leukocytes and liver of rats, reaching a steady state within 2-7 days of NDMA exposure¹⁰⁸. Importantly, the steady state DNA adduct levels were approximately linear related to NDMA dose-rate¹⁰⁸. NDMA-induced adducts are harmful as they cause mutations and stimulate unabated cell proliferation⁶³.

NDMA-induced tumors typically occur in tissues that have the ability to metabolize NDMA. The occurrence of tumors is related to the levels of cytochrome P450 (principally CYP2E1) within the cell and the ability of cells to metabolize NDMA by the alpha hydroxylation pathway. The cancer-causing activity of NDMA is directly dependent upon the cytochrome P450 (e.g., CYP2E1)-dependent metabolic conversion of NDMA to highly reactive molecules such as the methyldiazonium ion^{109,110}. In rat studies NDMA is shown to be metabolized primarily in the liver by an enzyme called cytochrome P450 2E1 (CYP2E1) to a methyldiazonium ion¹¹⁸. CYP2E1 is responsible for at least 60% of the NDMA-induced DNA methylation in rat hepatocytes¹¹¹. The cytochrome P-450 mixed-function oxidase system also metabolizes NDMA to a mutagen¹¹². Activation of NDMA to a mutagen is cytochrome P450 dependent¹¹². Importantly, mutations can lead to cancer. Thus, NDMA can induce tumors in any cells which express cytochrome P450

enzymes¹¹². NDMA is rapidly metabolized in any tissue that expresses the cytochrome P450 enzymes and can initiate cancer in that tissue. In addition, NDMA can act as a tumor-promoter to other sites in the body via the key characteristics and stimulate human cancer via inflammation, oxidative stress, immunosuppression, proliferation, cell death and angiogenesis (the growth of new blood vessels). Thus, NDMA can stimulate many cancer types including colorectal/intestinal, esophageal/pharyngeal, gastric, kidney, liver, lung, pancreatic, prostate, bladder and blood (e.g., lymphoma, leukemia and multiple myeloma) via metabolic activation, inflammation, angiogenesis, and the other key characteristics of carcinogens.

Even at low doses in the rat's drinking water, NDMA stimulated the formation of DNA adducts (e.g., O6-methylguanine) in the white blood cells (called leukocytes) and the liver within 2 to 7 days exposure¹⁷². Blood leukocytes are a reliable surrogate tissue for monitoring the biologically significant exposure to NDMA. NDMA causes DNA adduct formation and gene mutations (e.g., G:C to A:T) in various tissues such as the liver. NDMA-induced formation of O6-methylguanine in DNA is important in tumor initiation caused by NDMA. The formation of the DNA adduct N7-methylguanine is proportional to NDMA dose in the liver and kidney in rats orally administered NDMA. O6-methylguanine DNA adducts that accumulated over 28 days were linearly related to NDMA dose in the rat liver. The administration of NDMA in drinking water to rats also resulted in a dose-dependent increase of N7-methylguanine adducts in the liver at 28 days.

The probable human carcinogen formaldehyde can be formed from NDMA via chemical reactions (e.g., oxidation) with liver microsomes in rats, mice and hamsters^{112,113}. Additionally, the formaldehyde and acetaldehyde produced in the metabolism of NDMA are carcinogens. After NDMA treatment *in vivo* in animals or in tissue slices *in vitro*¹¹⁴⁻¹¹⁶, the major product was 7-methylguanine. In rats, even a single oral NDMA dose induces O6-methylguanine DNA adducts

in the kidney which parallels earlier findings in which oral or intraperitoneal administration of NDMA to rats increases the incidence of kidney tumors^{90,117}. Changes in DNA (e.g., G:C to A:T transitions) have been observed in the *ras* oncogene in mouse lung tumors induced by NDMA¹¹⁸. DNA methylation was studied in peripheral blood lymphocytes (PBLs) collected from Sprague-Dawley rats exposed to a single dose of NDMA¹¹⁹. The O6-meG-DNA adduct formation in PBLs and hepatocytes, at 2-24 h following the exposure to NDMA, was analogous for both types of cells¹¹⁹. In another study, DNA was extracted from livers, kidneys and lungs of Syrian golden hamsters at various times (up to 96h) after injection of a cancer causing dose of [14C]NDMA¹²⁰. At 7h after NDMA administration liver DNA was alkylated to the greatest extent, followed by that of the lung and kidney, O6-methylguanine was the most persistent alkylated purine in the hamster tissues¹²⁰.

DNA adducts are also generated by NDMA in large animals. In monkeys, orally dosed with 0.1 mg NDMA/kg body weight, the DNA adduct O6-methylguanine was detected in 32 tissues examined¹²¹. When monkeys were exposed to 0.1 mg/kg oral NDMA, the DNA adduct O6-methylguanine was detected in all tissues studied including stomach, esophagus, large intestine, small intestine, pancreas, liver, blood (white blood cells), ovary, bladder, spleen, brain (e.g. cerebellum, cerebrum, and brain stem), uterus, bone marrow, lymph nodes, prostate, adrenal, pituitary, skeletal muscle, kidney, heart muscle, heart blood vessels, skin, and lung¹²¹. The highest levels were in the gastric mucosa and liver with elevated levels also present in white blood cells which circulate throughout the body, the esophagus, ovaries, pancreas, bladder and uterus¹²¹. Thus, NDMA can cause cancer in all these tissues. Humans share over 90% of their DNA with their primate cousins the monkeys and chimpanzees¹²² and as one of our closest living evolutionary relatives, non-human primates (e.g. monkeys) are especially suited to teach us about ourselves.

The monkey species is widely used for biomedical research due to its high sequence similarity with humans (>93% for protein-coding genes)¹²³. Thus, monkeys provide meaningful scientific evidence on cancer formation mechanisms that applies to humans⁵⁰. NDMA also has been demonstrated to induce DNA adducts in various *human tissues* including liver, lung, bladder, colorectal/intestinal, pancreas, esophagus, buccal mucosa (the lining of the cheek), and placenta (an organ that develops in the uterus during a pregnancy)¹²⁴⁻¹³⁰. Thus, NDMA exposure to humans can form similar adducts throughout the human body to initiate cancer including these and other tissues including gastric, kidney, and blood.

In large animals (e.g., primates), low doses of NDMA given systemically caused the formation of DNA adducts (e.g., O6 methylguanine DNA adducts) in the esophageal tissue of oral mucosa. In monkeys, NDMA induced O6-methylguanine DNA adducts four hours post-administration in various tissues (e.g., kidney, esophagus, stomach, brain) similar to what was observed in the liver. This is unlike what is typically observed in rodents, in which adducts occurred primarily in the liver. To test if the fetus in primates is sensitive to the formation of cancer initiation-related DNA adducts, pregnant patas monkeys were given 1.0 or 0.1 mg/kg *NDMA*. Elevated levels of O6-methylguanine were detected in fetal liver, lung, kidney, spleen, brain, and placenta in a study in which pregnant patas monkeys were administered a single gastric NDMA dose of 1 mg/kg body weight (bw)¹³¹.

Human tissue and cells

This first key characteristic of NDMA was demonstrated in a human by the unfortunate case of poisoning, which was reported by Herron and Shank (1980)¹²⁶. A considerable amount of DNA methylation (O6-methylguanine and 7-methylguanine) was found in the victim's liver which evidenced that NDMA is metabolically activated in humans¹²⁶. DNA molecules in liver cells from

humans exposed to NDMA contain the methylated purines N7-methylguanine and O6-methylguanine, indicating alterations in DNA by NDMA. Human tissue (e.g. breast xenografts) also metabolize NDMA to active intermediates that react with DNA¹³².

This mode of action, and a crucial role of O-6methylguanine DNA-methyltransferase, is similar in rodents and humans (WHO, 2002). O-6methylguanine is the most potent premutagenic lesion induced by NDMA. Many tissues and cells in animals and humans metabolize NDMA including stomach, esophageal, pancreatic, bladder, liver, kidney, lung, prostate and leukocytes (white blood cells). In fact, in human lymphocytes, the identical DNA adducts as those observed in experimental animal studies are detected. In addition, adducts have been detected in human liver DNA following NDMA exposure¹²⁶. Thus, humans, like rodents, activate NDMA metabolically in an identical fashion as laboratory animals.

Importantly, metabolism of NDMA is similar in animals (e.g., rats) and humans, mediated by the identical enzyme, CYP2E1. NDMA metabolism in animals and humans is virtually identical, allowing scientists to conclude that NDMA is a human carcinogen. The mechanism of action of NDMA is related to metabolism by cytochrome P-450 enzymes to generate methyldiazonium ions and subsequent DNA adducts, predominantly N7-methylguanine and O6-methylguanine.

Conclusion – Key Characteristic #1

As cited above, there is overwhelming evidence that NDMA is metabolically activated via the formation of DNA adducts to cause cancer. The formation of DNA adducts such as O6-methylguanine is of critical importance in the cancer-causing activity of NDMA. Importantly, there is also convincing evidence that the biological activity of NDMA in humans does not differ to any meaningful degree from that in experimental animals and there is a human study that

confirmed a considerable amount of DNA methylation (O6-methylguanine and 7-methylguanine) in the victim's liver¹²⁶. As such, we can predict with a high degree of confidence that NDMA is carcinogenic in humans. Thus, NDMA requires metabolic activation to exert its cancer causing activity.

It is biologically plausible that NDMA causes cancer via key characteristic #1.

Carcinogen Key Characteristic #2: NDMA is Genotoxic

General Description

Genotoxicity is defined as the capability of a chemical to cause DNA damage, alter the genome (mutation), or both²⁵. Mutagens are agents that damage DNA and can, depending on the ability of an organism to repair DNA damage, lead to permanent changes (mutations) in the DNA sequence. Clastogenic is a mutagen that results in sections of chromosomes being deleted, added, or rearranged. This process is a form of mutagenesis which can lead to cancer. The term “genotoxic” refers to an agent that induces DNA damage, but this damage may or may not necessarily be processed by the cell into a mutation. If an agent is found to induce DNA damage, it is a genotoxin, and if it is shown that the agent also induces mutations in a mutagenicity assay, it can be classified as a mutagen.

Why is genotoxicity important to the mechanism of carcinogenesis?

The link between genotoxicity and cancer causation is well-established as cause and effect and has shaped standardized testing of carcinogens for decades¹³³. Genotoxicity can arise from DNA strand breaks, DNA adducts, DNA-DNA crosslinks, and DNA-protein crosslinks, as well as from oxidative damage to DNA (which is also relevant to key carcinogen characteristic #5)²⁴. It is very important to perform genotoxicity studies to avoid human exposure to the potential DNA

damage that can be caused by genotoxic carcinogens. Mutagenesis (the formation of mutations in DNA molecules) is driven by DNA damage resulting from genotoxicity.

Genotoxicity in animal tissues and cells

There is overwhelming evidence that NDMA is genotoxic, mutagenic and clastogenic (IARC, 1978). NDMA is a well-studied prototype genotoxic carcinogen which binds directly to DNA generating DNA adducts, DNA damage, and mutations¹³⁴. NDMA has been classified as a genotoxic carcinogen by the European Union (ISZW99). NDMA exhibits genotoxic activity in standard assays such as the Ames assay and the Comet assay. Many studies show that NDMA is genotoxic both *in vivo* and *in vitro*. Increased frequencies of gene mutations, chromosomal damage, sister chromatid exchange and unscheduled DNA synthesis have been observed in a wide variety of cell types and assays. Clear evidence of genetic effects has also been observed in *in vivo* studies. Clastogenic effects (e.g., micronuclei, sister chromatid exchange, chromosomal aberrations) in hepatocytes¹³⁵⁻¹³⁷, bone marrow cells^{138,139}, spleen cells¹⁴⁰, and peripheral blood lymphocytes¹³⁶, as well as in esophageal¹⁴¹ and kidney cells¹⁴², have been observed in rodents (rats, mice or hamsters) administered NDMA either orally or by intraperitoneal injection.

Increased frequencies of micronucleated cells were observed at NDMA doses as low as 5 mg/kg body weight in rats¹⁴¹. Effects in germ cells (e.g., micronucleated spermatids) were observed in mice given 6 or 9 mg NDMA/kg body weight via intraperitoneal injection¹⁴³. The inhalation exposure of female mice to NDMA at 1030 mg/m³ increased the frequency of micronucleated bone marrow cells¹⁴⁴. Evidence of genotoxicity (e.g., chromosomal aberrations, micronuclei, gene mutation, DNA strand breaks) has also been observed in the offspring of hamsters¹⁴⁵ and mice¹⁴⁶ administered NDMA during gestation. Numerous publications have demonstrated that in rodents (rats, mice or hamsters) administered NDMA either orally or by

intraperitoneal injection, evidence of DNA damage has been observed in many tissues throughout the body including liver, kidneys and lungs¹⁴⁷⁻¹⁶². DNA damage in the thymus¹⁴⁸, sperm¹⁵⁴, and nasal and tracheal cells¹⁵⁶ has also been observed. NDMA was also mutagenic at the *lacI* locus (in the liver) in *in vivo* assays involving transgenic mice¹⁶³⁻¹⁶⁵. In addition, increased unscheduled hepatic DNA synthesis has been observed in rats at NDMA doses as low as 0.1 mg/kg bw¹⁵⁰. In mice, NDMA caused an increase in mutations (e.g., 10-20 fold) that increased with time and the number of treatments^{163,164}.

The NDMA-induced genotoxic effects and DNA damage in cancer cells generate reactive oxygen species which can lead to further DNA strand breaks and oxidative DNA damage (which synergizes with key characteristic #5) to initiate and promote cancer. Genotoxicity induced by NDMA is further demonstrated in extrahepatic (outside the liver) tissues of rats by the persistence of DNA damage in the lung, liver, kidney and nasal cavity^{158,159,166}. Remarkably, two notable studies observed genotoxicity in the offspring of animals exposed to NDMA¹⁶⁷. When nursing Sprague-Dawley rats were treated with radiolabeled NDMA and other nitrosamines, the liver and kidney DNA from their 14-day-old offspring that had been nursed over a 24-hour period became labeled with the NDMA and other nitrosamines. Notably, upon analysis, liver DNA from the offspring whose nursing mothers were treated with the radiolabeled NDMA showed N7-methylguanine and O6-methylguanine DNA adducts¹⁶⁷.

Importantly, NDMA is such a potent genotoxic carcinogen that it does *not* exhibit a no-observed-adverse-effect level (NOAEL) as demonstrated by studies including Peto *et al.*¹⁹. The NOAEL is defined by the level of exposure of an organism, found by experiment or observation, at which there is no increase in the frequency or severity of any adverse effects (e.g., cancer incidence) of the tested protocol. In Peto *et al.* there was no indication of any threshold

for tumor induction. NDMA at 0.1 ppm in drinking water caused about 2.5% of animals to develop liver tumors and therefore a dose of 0.01 ppm would yield a 0.25% incidence.

NDMA causes genotoxicity in large animals

NDMA causes genotoxicity (DNA damage) in a wide spectrum of tissues in the monkey, with at least eight tissues sustaining DNA damage levels with 50% of those of the liver¹²¹. Among these tissues are included common sites of human cancer such as the large and small bowel, the pancreas and the esophagus. Four hours after NDMA exposure, DNA adducts (O6-meG) are expressed in all tissues including gastric mucosa, liver, white blood cells, esophagus, ovary, large intestine, bladder, spleen, uterus, and brain¹²¹. In the diet, DNA adducts from NDMA (e.g., O6-meG) were found in blood cell DNA, at levels ranging 0.02–0.12 fmol mg DNA. To quote from this publication ***“It is evident, that in contrast to rodents, these important cancer targets share with liver an equal likelihood of sustaining DNA damage after NDMA exposure¹²¹.”*** Thus, NDMA can lead to cancers and genotoxic damage in many organs and target tissues¹²¹.

Human tissue and cells

Two studies by Hakura *et al.* found that fractions from human cells were considerably more active than those from rats in stimulating the mutagenic response to NDMA in the Ames test: the mutation rate was up to 8 times higher with some human S9 fractions^{168,169}. The recent observation that human S9 fractions are much more active than rat S9 fractions in promoting genotoxicity in the Ames test suggests that humans may be especially sensitive to the carcinogenicity of NDMA^{168,169}. Thus, the genotoxicity of NDMA has been extensively proven in animal models as well as animal and human tissue.

Importantly, human tissues (e.g., liver, kidneys, lung, and digestive tract) metabolize NDMA into genotoxic DNA adducts. Seven different human tissues such as trachea, lung,

esophagus, colon, pancreas, bladder, and buccal mucosa can metabolize NDMA into cancer causing metabolites (e.g., reactive electrophiles- a key characteristic of carcinogens). Human tissues such as human lung (e.g., bronchi), colon and esophagus metabolize NDMA into reactive electrophilic metabolites that react with cellular DNA and protein leading to carcinogen DNA adducts (e.g., alkylated DNA in both O-6 and N-7 position of guanine). Both human liver and lung can metabolize NDMA *in vitro*. Montesano and Magee reported that slices of human liver can metabolize radio-labeled (^{14}C) NDMA into (^{14}C)CO₂ and intermediates that alkylate bases in nucleic acids forming primarily 7-methylguanine¹²⁵. Slices of human lung can metabolize (^{14}C) NDMA, as measured by production of (^{14}C)CO₂. (^{14}C)NDMA binds to both DNA and protein of cultured human bronchi. Binding to DNA was NDMA dose-dependent. NDMA results in methylation of DNA at both the O-6 and N-7 positions of guanine in human cells. NDMA induced O-6 methylation of DNA in cultured human bronchia. Thus, human tissues (e.g., lung tissue) can metabolize NDMA into reactive intermediates.

The cellular and molecular changes induced by nitrosamines (e.g., NDMA) in animals are similar to those in human tissues. Repair of DNA lesions such as O6-methylguanine occurs in other tissues besides the liver. Thus, the cancer-causing mechanisms which occur in animals also take place in humans. The metabolism of NDMA and NDEA as measured by alkylation of DNA is similar in the rat and human esophagus as well as extrahepatic tissues.

NDMA is genotoxic in various human tissues (e.g., liver, colon, bronchi, and esophagus) in cultured cells. DNA molecules in liver cells from humans intoxicated with NDMA contained the methylated purines N7-methylguanine and O6-methylguanine, indicating alterations in DNA caused by NDMA. Liver cancer cells are capable of metabolizing NDMA to genotoxic products.

NDMA induces a dose-dependent increase in the frequency of DNA single-strand breaks and alkali-labile sites in primary cultures of rat lung cells and in lung cells from human donors.

Conclusion – Key Characteristic #2

Abundant studies have demonstrated potent genotoxic activity of NDMA in numerous *in vivo* and *in vitro* assays, including with human cells. Thus, studies with human cells, as well as studies of animals and microbes, clearly demonstrate the genotoxicity activity of NDMA.

It is biologically plausible that NDMA causes cancer via key characteristic #2.

Carcinogen Key Characteristic #3: NDMA Alters DNA Repair and Causes Genomic

Instability

General Description

Normal cells try to avoid deleterious mutations by replicating their genomes with high accuracy. Most spontaneous mutations are caused by polymerase error¹⁷⁰. The nature of the mistake, the presence of DNA damage, and the ability to correct errors all have an impact on the outcome of this process. As a consequence, defects in processes that determine DNA replication fidelity can confer strong mutator phenotypes that result in genomic instability. Thus, carcinogens may act not only by producing DNA damage directly but also by altering the processes that control normal DNA replication. Different susceptibilities of organs to carcinogenic stimuli may be determined by the ability to repair certain alterations produced by the carcinogen in DNA¹⁰².

Why is genomic instability important to the mechanism of carcinogenesis?

DNA damage is a source of genomic instability without correct DNA repair. DNA repair is critical for cancer prevention as DNA repair prevents the genetic mutations in normal cells¹⁷¹. While DNA excision repair pathways are predominantly error-free and thus protective, double-strand break repair is largely error-prone and may contribute to genomic instability. Genomic

instability is a well-recognized hallmark of many cancers and is considered to be one of the enabling characteristics of cancer¹⁰¹. Markers of genomic instability include chromosome aberrations, gene mutations, microsatellite instability, and apoptosis²⁴. The ability of cells to repair DNA adducts (by removing *O*-methylguanine through the action of a specific *O*-methylguanine DNA-methyltransferase) prior to cell division likely plays a critical role in determining the susceptibility of tissues to tumor development.

NDMA alters DNA repair and causes genomic instability.

The ability of the tissue to repair DNA adducts plays an important role in the mechanism of NDMA causing cancer. Importantly, NDMA alters DNA replications and promotes subsequent DNA damage, thereby priming cells for carcinogenesis. The rate of elimination of DNA adducts may be an important factor in neoplastic transformation by alkylating carcinogens. Following administration to rats of various doses of NDMA, O6-methylguanine (O6-meG) was lost from the DNA of four tissues (liver, white blood cells, lymph nodes, bone marrow). NDMA alters DNA repair enzymes (e.g., AGT) with DNA leading to genomic instability. Following the administration of NDMA, alkylation of DNA occurs in both the liver and kidney but the adducts are more persistent in the kidney. O6-methylguanine-DNA transferase (MGMT) is an enzyme that repairs O6-methyl guanine and other O6-alkyl guanine DNA adducts. Repair of DNA by MGMT (or lack of repair) has a key role in the development of NDMA-induced cancer. A single dose of NDMA induces the inability of the kidney to rapidly repair DNA methylation leading to kidney tumors.

Human tissue and cells

Consistent with carcinogen key characteristics #1 and #3, DNA adducts from NDMA are repaired very slowly in human blood, hence, these DNA adducts can build up in the blood. Intra- and intercellular variations occur in the repair efficiency of O6-methylguanine in human liver

cancer cells (HepG2 cells) treated *in vitro* with NDMA¹⁷². MGMT, the enzyme responsible for the repair of O6-methylguanine DNA adducts, has been detected in the liver of humans. Thus, NDMA results in DNA alkylation adducts which are not repaired correctly leading to cancer.

Conclusion – Key Characteristic #3

NDMA alters the processes that control normal DNA replication or repair of DNA damage. Thus, NDMA induces genomic instability with an increased risk for DNA mutations and other genetic changes during cell division. As a result, NDMA is a probable human carcinogen via alterations in DNA repair capacity and genomic instability.

It is biologically plausible that NDMA causes cancer via key characteristic #3.

Carcinogen Key Characteristic #4: NDMA Induces Epigenetic Alterations (e.g., DNA Methylation)

General Description

The term “epigenetic” refers to all stable changes in gene expression and chromatin organization that are independent of the DNA sequence itself and that can be mitotically inherited over cell divisions. Epigenetic phenomena include genomic imprinting, changes in chromatin and histone modification patterns. Epigenetic alterations are changes in gene expression including DNA methylation. Carcinogens can induce epigenetic changes which can lead to cellular transformation. Epigenetic changes initiate and mediate cancer progression.

Why are epigenetic alterations (e.g., DNA methylation) important to the mechanism of carcinogenesis?

A wide range of known and suspected carcinogens (including chemical, physical, and biological agents) have been shown to deregulate the epigenome.

NDMA epigenetic alterations in animal tissues and cells

NDMA-induces epigenetic alterations in the animal studies. In rats, independent of dose and route of administration, NDMA induced DNA methylation (e.g., N7Guanine and O6Guanine) in whole tissues (e.g., liver and nasal mucosa) after a single injection of NDMA. Several independent studies from various laboratories have demonstrated that NDMA induces DNA methylation in rats¹⁷³⁻¹⁷⁵. The induction of microsomal NDMA demethylase activity was closely related to the increase of DNA methylation by NDMA¹⁷⁶.

DNA methylation can mediate the pro-tumorigenic and cancer-initiating activity of NDMA. The rat nasal mucosa contains relatively high levels of cytochrome P-450 enzymes and these enzymes can catalyze the alpha-hydroxylation of NDMA.

Conclusion – Key Characteristic #4

NDMA may disrupt epigenetic mechanisms as a human carcinogen via DNA methylation.

It is biologically plausible that NDMA causes cancer via key characteristic #4.

Carcinogen Key Characteristic #5: NDMA Induces Oxidative Stress*General Description*

Reactive oxygen species (ROS) are compounds that cause oxidative damage to cellular biomolecules. Oxidative stress including reactive oxygen and nitrogen species (RONS) critically mediate cancer progression by carcinogens and pathogens^{171,177}. ROS are important mediators of oxidative stress. An imbalance between formation of reactive oxygen and/or nitrogen species and their detoxification is commonly referred to as oxidative stress. ROS, which can arise from inflammation, may contribute to genomic instability and, along with other free radical species, play key roles in many of the processes identified as being necessary for the conversion of normal cells to cancer cells^{13,25}. Oxidative stress can lead to oxidative damage to DNA¹⁷⁸. Oxidative stress

is directly related to many other key characteristics of carcinogens, notably #2 and #3 via DNA damage leading to genotoxicity and alteration of DNA repair, as well as others including chronic inflammation (#6) and altered cell proliferation (#10)²⁵. Oxidative stress is also a common occurrence in cancer and can be a critical component of the tumor microenvironment. Oxidative damage is considered a major factor in the generation of mutations in DNA, and greater than one hundred different types of oxidative DNA damage have been identified to date¹⁷⁸. Oxidative damage to DNA may initiate or promote carcinogenesis¹⁷⁸.

Why is oxidative stress important to the mechanism of carcinogenesis?

Experimental, clinical and epidemiological studies have provided compelling evidence that oxidative stress is critical in the initiation and progression of cancer. Oxidative stress causes cellular and molecular events that can cause and promote cancer by causing an imbalance between production and accumulation of ROS in cells and tissues and the ability of a biological system to detoxify these reactive products. ROS can trigger genomic instability. Oxidative damage to DNA can lead to point mutations, deletions, insertions, or chromosomal translocations, which can cause activation of oncogenes and inactivation of tumor suppressor genes, potentially leading to initiation of carcinogenesis. Oxidative stress, reactive chemical species (e.g., ROS), and proliferation stimulate DNA damage and inhibit DNA repair to stimulate tumor progression.

NDMA induced oxidative stress in animal tissues and cells

NDMA induces oxidative stress including oxidative damage to both DNA and lipids^{179,180}. NDMA stimulates ROS and induces a dramatic change in the body weight of animals leading to toxicity. NDMA can cause cancer via an aggressive positive feedback loop between oxidative stress, inflammation, DNA damage, and carcinogenesis. NDMA stimulates inflammation-mediated DNA damage.

NDMA triggers metabolites which can produce mutations in DNA via oxidative stress. This results in high amounts of oxidative stress and production of ROS that further contributes to organ damage and cell death. NDMA stimulates oxidative stress and lipid peroxidation that enhances necrosis (cell death), which initiates mitosis and hepatic regeneration. Thus, NDMA injures cells in various organs and throughout the human body in multiple ways to trigger inflammation via oxidative stress and ROS. The formation of 8-OHdG can be one of the causes of point mutations that contribute to the activation of oncogenes or the inactivation of suppressor genes leading to cancer.

The toxic effect of NDMA greatly influences the biological activity and lifespan of immune cells, including neutrophils, by inducing a respiratory burst and subsequent release of ROS which stimulates oxidative stress. Oxidative stress can stimulate proliferation of tumor cells acting in synergy with genotoxic mechanism including mutations to cause cancer. Oxidative and endoplasmic reticulum (ER) stress stimulates apoptotic cell death and survival factors contributing to the persistent cycle of cell death and tissue regeneration (“Phoenix Rising” pathway) which can lead to tumor repopulation and persistent tumor growth. Chronic inflammation and pro-inflammatory cytokines generated by immune cells in the human body cause hyperplasia, oxidative stress, and act synergistically with DNA damage to drive carcinogenesis. Carcinogens induce reactive oxygen and nitrogen species resulting in oxidative stress and inflammation.

Conclusion – Key Characteristic #5

Thus, NDMA can be a human carcinogen by stimulating oxidative stress via oxygen radical-induced cellular injury.

It is biologically plausible that NDMA is a human carcinogen via oxidative stress - key characteristic #5.

Carcinogen Key Characteristic #6: NDMA Stimulates Chronic Inflammation*General Description*

The relationship between inflammation and cancer dates back to 1863 when Rudolf Virchow suggested that chronic inflammation from tissue injury stimulates the proliferation of cells leading to cancer¹⁸¹. Many experimental studies including those from my laboratory have indeed confirmed that inflammation can stimulate or induce tumor initiation, growth, and metastasis^{6-10,13,33,182-186}. Inflammation in the tumor microenvironment is now known as a hallmark of cancer¹⁰¹ and is recognized as a key characteristic of carcinogens^{24,25}.

Why is chronic inflammation important to the mechanism of carcinogenesis?

Inflammation triggers escape from tumor latency and tumor dormancy¹⁸⁷. Inflammation is a critical driver of cancer and metastasis which can occur throughout the entire body. Chronic inflammation including signaling from pro-inflammatory cytokines triggers oxidative stress and genotoxicity leading to DNA damage and cancer cell proliferation. Thus, inflammation can synergize with DNA damage to promote cancer growth. Chronic inflammation also acts as a tumor promoter in various malignancies such liver, prostate, pancreatic, colorectal (CRC), gastric, gallbladder, and esophageal cancers^{185,188,189}. My laboratory has also recently demonstrated that chronic inflammation acts as a tumor promoter^{6,7,10,11}.

NDMA induces chronic inflammation in animal tissues and cells

Inflammation, an initial stage of cancer (e.g., cholangiocarcinoma), can be induced in hamsters exposed to NDMA and a human liver fluke infection¹⁹⁰. NDMA-induced cancer tissues showed significantly higher numbers of inflammatory cells, especially eosinophils, bile duct proliferation and IL-17+ inflammatory cell infiltration compared to normal livers¹⁹⁰. NDMA-induced cholangiocarcinoma in hamsters resulted from increased pro-inflammatory molecules

such as high mobility group B1 (HMGB1), interleukin-8, and 8-OxodG (oxidative DNA damage marker) in the cancer tissues¹⁹¹. HMGB1 is a potent pro-inflammatory factor that can initiate and stimulate inflammation¹⁹².

NDMA can also act as a tumor-promoter in bile duct cancers that are initiated with either infection by *Helicobacter pylori* or *Opisthorchis viverrini* (liver fluke)¹⁹¹. A study by Thamavit showed that 12.5% of hamsters receiving 12.5 ppm of NDMA in drinking water alone exhibited tumors, and 50% of hamsters receiving NDMA plus *O. viverrine* infection developed tumors by 40 weeks¹⁹³. In multiple studies in Syrian hamsters, NDMA stimulates inflammation in the bile ducts^{194,195}. Histopathologic analysis of bile duct tissues from hamsters treated with NDMA showed a high number of inflammatory cells^{194,195}. NDMA induced the infiltration of inflammatory cells around the bile ducts and liver at days 30 and 60¹⁹⁵. Similarly, NDMA administration in rats induces chronic inflammation and liver tumors⁷⁴. In rats, NDMA-induced inflammation from an increase in inflammatory cells called neutrophils induces liver fibrosis¹⁹⁶, which can also act as a tumor promoter. Pro-inflammatory molecules such as connective tissue growth factor (CTGF), α -SMA, type I collagen, MMP-2, and MMP-9 were markedly increased in NDMA-treated mice¹⁹⁷.

NDMA can also induce liver fibrosis in mice that is similar to fibrosis observed in humans through the generation of oxyradicals, which can stimulate tumor growth. NDMA-induced fibrosis leads to oxidative stress and generation of reactive oxygen species, which can promote tumor growth. These processes lead to cellular injury and inflammation that trigger activation and transformation of hepatic stellate cells into myofibroblast-like cells, which initiates excessive synthesis of connective tissue proteins, especially collagens. Uncontrolled and extensive fibrosis results in distortion of lobular architecture of the liver leading to nodular formation and cirrhosis.

The perpetual injury and regeneration process can also result in genomic aberrations and mutations that lead to the development of various cancers including bladder, liver and prostate. NDMA triggers the immune system and activates lymphocytes which in turn produce various pro-inflammatory cytokines such as IL-1 β , IL-6, IL-22, interferon- γ (IFN- γ), and TNF- α . The pro-inflammatory cytokines trigger hepatocytes to activate downstream pro-tumorigenic molecular signaling pathways such as NF-kB and TGF- β .

Human tissue and cells

In human cells called human H69 cholangiocytes, NDMA stimulates the pro-inflammatory enzyme cyclooxygenase 2 (COX-2), which can generate pro-inflammatory lipid molecules called eicosanoids¹⁹⁸. Cholangiocytes are epithelial cells that line the bile ducts, which are small tubes that carry bile from the liver. COX-2 over-expression has been observed in various inflammatory diseases and can be strong promoter of cancer via inflammation¹⁹⁸. In human white blood cells (called peripheral blood mononuclear cells), NDMA stimulates several pro-inflammatory and pro-tumorigenic mediators including TNF- α , IL-1, GM-CSF, and VEGF. NDMA activates mitogen-activated protein kinases (MAPK) in human white blood cells, which promotes cell proliferation and cancer progression.

Conclusion – Key Characteristic #6

NDMA functions as a tumor promoter by stimulating chronic inflammation. Strong interdependent links exist between inflammation, genotoxicity and the induction of oxidative stress and genomic instability. Because NDMA stimulates all of these key characteristics, these mechanisms can act synergistically with chronic inflammation to cause and promote cancer. Thus, NDMA is a human carcinogen.

It is biologically plausible that NDMA is a human carcinogen via chronic

inflammation - key characteristic #6.

Carcinogen Key Characteristic #7: NDMA is Immunosuppressive (e.g., inhibits B and T lymphocytes)

General Description

Immunosuppression is a reduction in the capacity of the immune system to respond effectively to foreign molecules including those on tumor cells. Immunosuppression differs from other mechanisms of carcinogenesis in that immunosuppressive agents may not directly transform normal cells into potential tumor cells²⁴. However, they can promote tumor growth synergistically with other processes that directly transform cells. A classic example of an immunosuppressive drug given before organ transplant (e.g., kidney transplants) is cyclosporine. Epidemiological data from patients with congenital immunodeficiencies, virally induced immunodeficiencies (e.g., HIV-mediated), and from patients treated with immunosuppressive therapies (e.g., organ transplant rejection prevention therapies such as cyclosporine) show that profound immunosuppression is associated with an increased cancer risk²⁴.

Why is immunosuppression important to the mechanism of carcinogenesis?

The immune system in the human body normally functions to protect against invading pathogens and eliminate cancers. Immune cells typically have the ability to detect specific markers on potential tumor cells and clear them before cancer is initiated. Thus, chemicals that cause immunosuppression can increase the risk of cancer and persistent immunosuppression can cause or stimulate cancer.

NDMA induced immunosuppression in animal tissues and cells

In mice, chronic exposure to NDMA induced a marked and persistent immunosuppression of cellular and humoral responses in mice¹⁹⁹. Cellular immunity protects the body from cancer via the activation of immune cells called phagocytes, T cells and the release of cytokines in response to an antigen on a tumor cell. Humoral immunity protects the human body from cancer via substances found in the humors, or body fluids. Chronic exposure to NDMA induces immunosuppression via a reduced cellular and humoral immune response in mice. The persistent NDMA-induced immunosuppression could be reversed after the removal of NDMA from the drinking water.

In mice, NDMA induced suppression of the protective antibody response to a T-cell-dependent antigen, and the lymphoproliferative response to the T-cell and the B-cell mitogens in a dose-dependent manner²⁰⁰. Exposure of mice for 14 days to NDMA by intraperitoneal injection resulted in depressed T-lymphocyte function as measured by T-cell proliferation and suppressed IgM antibody-forming cell response in a dose-dependent manner. NDMA-exposed animals exhibited immunotoxicity via reduced humoral antibody responses, T-cell mitogenesis, and bactericidal activity. NDMA suppressed various measures of humoral immunity. NDMA suppressed the IgM antibody-forming cell response to sheep red blood cells (on day four) in a dose-dependent manner. Reduced host resistance to infectious agents (reduced response to streptococci and influenza challenge) following NDMA administration also indicated suppressed effects on humoral immunity. NDMA blocked T-lymphocyte function as measured by T-cell proliferation. NDMA exhibits immunotoxic effects *in vitro* and in various animal models.

In vivo studies have shown that NDMA modulates the cellular immune response by altering the production and/or maturation/differentiation of bone marrow stem cells into functional macrophages. One of the primary cell targets of NDMA is the B-lymphocyte, which normally generates antibodies that protect the body from cancer. NDMA suppressed IgM antibody-forming

cell response to sheep red blood cells after only 4 days in a dose-dependent manner. Splenocyte proliferation in response to lipopolysaccharide, an inflammatory molecule, was also suppressed by NDMA administration, showing an impaired immune response by NDMA. Thus, NDMA decreases the overall reactivity of both T- and B-lymphocytes, which are important to protect from cancer. NDMA suppressed various measures of humoral immunity. Cellular immune response, monitored by stimulation of cells in mixed lymphocyte reaction (MLR), was markedly suppressed by NDMA, suggesting increased cancer progression due to chronic immunosuppression.

Human tissue and cells

In addition to experimental animal evidence, human studies also support adverse effects of NDMA on certain immune functions. In human blood cells called neutrophils, NDMA activates the pro-cancer PI3K-Akt/PKB and immunosuppressive pathway, which in turn, contributes to the activation of pro-inflammatory transcription factors NF- κ B, c-Jun, and FosB²⁰¹. The expression of Bax and Mcl-1 proteins in autologous peripheral blood mononuclear cells (PBMCs) results in impairment of white blood cell (e.g., leukocyte) function in persons exposed to NDMA. NDMA alters humoral immunity and antibody-mediated host defense mechanisms. White blood cell differentials are indicators of the ability of the body to eliminate infection. A reduction in neutrophils can indicate that the ability of the body to attack and destroy invading bacteria, viruses, and other injurious agents (via phagocytosis) is compromised.

Conclusion – Key Characteristic #7

Thus, NDMA can disrupt the normal host immune response, which would usually protect from cancer progression. The ability of NDMA to be immunosuppressive contributes to its pro-carcinogenic activity. Thus, NDEA notably reduces immunosurveillance²⁰² and causes dysfunction of the immune system, and thereby plays a critical role in carcinogenesis.

It is biologically plausible that NDMA causes cancer via immunosuppression, key characteristic #7.

Carcinogen Key Characteristic #8: Modulates Receptor-Mediated Effects

Numerous carcinogens act as ligands to receptor proteins. Receptor-mediated activation broadly falls into two categories: *a*) intracellular activation, mediated by nuclear receptors that translocate into the nucleus and act on DNA as transcription factors, and *b*) activation of cell surface receptors that induce signal-transduction pathways resulting in biological responses that involve a variety of protein kinases²⁴. Molecular pathways that are regulated through ligand-receptor interaction and are most relevant to carcinogenesis include cell proliferation (e.g., stimulation of the normal proliferative pathways, as is the case for estrogen-dependent tissues and hormone therapy), xenobiotic metabolism, and apoptosis²⁴.

The carcinogen NDMA receptor-mediated activity has not been characterized. Receptor-mediated effects can occur at the cell surface (through ligand-binding) or intracellularly (via the disruption of signaling cascades or actions on nuclear/cytosolic receptors), all of which can modulate transcriptional changes in the nucleus. Thus, since both receptor binding and receptor functional activity of NDMA have not been characterized, it is unknown if NDMA exhibits this characteristic.

Carcinogen Key Characteristic #9: NDMA Causes Immortalization By Transforming

Normal Cells Into Cancer Cells.

General Description

Cancer cells are immortal, and therefore have limitless replicative potential and can divide non-stop. Normal (non-cancer) cells have a limited lifespan and will stop dividing. Immortalization is associated with stemness, the ability of cells to self-replicate indefinitely.

Why is immortalization important to the mechanism of carcinogenesis?

Cancer cells are immortal and undergo proliferation. If the cancer cells are dividing more rapidly, it means the cancer is faster growing or more aggressive. The rate of cancer cell proliferation can be estimated by doing a Ki-67 test for proliferation. The opposite of immortalization is cellular senescence, a cellular program in which cells stop dividing. Chemical carcinogens including tobacco, PCBs and asbestos promote immortalization and inhibit senescence.

NDMA induced immortalization in animal tissues and cells

NDMA is a carcinogen and is highly toxic to experimental animals by causing severe liver injuries and cancers¹⁹¹. NDMA reacts with rapidly proliferating cells in the terminal end buds of cellular DNA forming DNA adducts, which transform normal terminal end buds to cancer²⁰³. Thus, NDMA induces cell transformation from non-malignant cells to cancer cells¹⁹⁸. In *in vitro* studies, nitrosamines including NDMA can transform normal cells (e.g., fibroblasts) into cancer cells. The mutagenic potential of nitrosamines can be measured using a cell transformation assay *in vitro*, and nitrosamine mixture including NDMA caused a malignant transformation in NIH3T3 fibroblast cells to cancer cells²⁰⁴. NIH3T3 cells were used due to their wide applicability in cell malignant transformation studies²⁰⁴. As stem cells can play a role in cell transformation, NDMA and other nitrosamines can induce damaged cells in the stem cell region of the small bowel^{205,206}.

Human tissue and cells

In human cells called H69 cholangiocytes (bile duct cells), NDMA can induced the transformation of normal H69 cells to cancer-like cells via the overexpression of pro-tumorigenic molecules Cy19, Ki-67 and COX-2.

Conclusion – Key Characteristic #9

NDMA can immortalize the non-tumor (normal) cell into tumor cells.

It is biologically plausible that NDMA causes cancer via immortalization- key characteristic #9.

Carcinogen Key Characteristic #10: NDMA Alters Cell Proliferation, Cell Death or Nutrient Supply (e.g., Angiogenesis)

General Description

Sustained cellular proliferation is a key factor in cancer progression. As summarized in the United States Environmental Protection Agency guidance assessing risk of cancer from early-life exposures (EPA, 2005), more frequent cell division during development can result in enhanced fixation of mutations because of the reduced time available for repair of DNA lesions, while clonal expansion of a mutated cell produces a larger population of mutant cells²⁵. Cell death releases pro-inflammatory signals into the surrounding tissue microenvironment, resulting in recruitment of inflammatory cells of the immune system that can participate in tumor promotion through their influence on cancer cell proliferation and invasiveness. Angiogenesis, in which new blood vessels grow into a tumor, is key to providing nutrients to the cancer. Tumor growth requires angiogenesis to grow¹.

Why is alteration of cell proliferation, cell death or nutrient supply (angiogenesis) important to the mechanism of carcinogenesis?

Cell proliferation: Abnormal proliferation can allow transformed cancer cells to evade usual checkpoints and to continue replication.

Cell death: Apoptotic and necrotic cell death releases pro-inflammatory signals into the surrounding tissue microenvironment, recruiting inflammatory immune cells to the site of trauma, which can enhance cancer-cell proliferation and promote cancer metastasis. In addition, my laboratory recently demonstrated that cell death generated by carcinogens as well as cancer therapy (e.g., chemotherapy and radiation) paradoxically stimulate the growth of surviving tumor cells via inflammation and a storm of pro-inflammatory and pro-angiogenic molecules.

Angiogenesis: Tumor growth is dependent on angiogenesis, the formation of new blood vessels¹. Tumor angiogenesis is stimulated by angiogenic growth factors that stimulate blood vessel growth. For example, pro-angiogenic factors (e.g., CXCL-8/IL-8) and vascular endothelial growth factor (VEGF) stimulate tumor growth and tumor dormancy escape.

NDMA alters cell proliferation, cell death, or nutrient supply (e.g., angiogenesis) in animal tissues and cells

In Syrian hamsters, NDMA stimulates proliferation of cells (e.g., from the bile duct), as confirmed with an increase in a proliferation marker called proliferating cell nuclear antigen (PCNA)¹⁹⁴. RNA analysis using a technique called quantitative real time PCR confirmed NDMA-induced proliferation with cell proliferating genes (e.g., telomerase and c-Ski)¹⁹⁴. Stimulation of cell proliferation is important in the induction of mutations or cancer by NDMA^{207,208}.

A single dose of NDMA causes massive activation of pro-apoptotic (cell death) mechanisms. NDMA induces cell death which can lead to tumor-promoting inflammation. NDMA induces apoptotic cell death via CYP2E1-catalyzed metabolism of NDMA²⁰⁹. The metabolites of NDMA trigger apoptotic cell death in these P450-expressing cells²⁰⁹. The metabolism of NDMA

in the CYP2E1-expressing cell line, GM2E1, causes both DNA methylation and oxidation and support that NDMA-mediated DNA damage plays a key role in NDMA-induced cancer²¹⁰. Hydroxydeoxyguanosine (8-OHdG), a biomarker for oxidative DNA damage, was stimulated by NDMA and lowered by administration of ascorbic acid²¹⁰.

NDMA induces the apoptosis (cell death) of neutrophils and PBMC (human macrophage). NDMA also results in cytotoxic activity and apoptosis in various organs (e.g., large bowel). Oxidative stress (key characteristic #5) plays a key role in the NDMA-induced cell death. Cell death induces a pre-cancer “Phoenix rising pathway” that can stimulate tumor growth. Paradoxically, cell death can stimulate tumor growth via inflammation, pro-inflammatory cytokines and bioactive lipid mediators.

In a bile duct (cholangiocarcinoma) cancer model, NDMA stimulated angiogenesis, the formation of new blood vessels and microvessel density via pro-angiogenic and lymphangiogenic factors (e.g., VEGFC) and their receptors (VEGFR3)²¹¹. This was associated with high VEGFR3 and VEGFC which was significantly associated with angiogenesis and metastasis in human cancer tissues from bile duct cancer patients²¹¹. Thus, NDMA stimulates angiogenesis and cancer spread (e.g., metastasis) in bile duct cancers.

Human tissue and cells

In human cholangiocyte cells of the bile duct, NDMA increases the turnover (proliferation) of cells and the proliferation marker called Ki-67¹⁹⁸. NDMA induces apoptotic cell death of various cells such as human white blood cells (e.g., leukocytes). The pro-apoptotic effects of NDMA were confirmed in human leukocytes indicate an active participation of the cell death molecules TRAIL/DR5 complex and Fas protein²¹². NDMA can also induce the apoptosis of human

neutrophils by regulating the expression of death receptor DR5 as well as through the release of its soluble form (sDR5).

Conclusion – Key Characteristic #10

Thus, NDMA can act as a tumor promoter via stimulating these 3 processes: cell proliferation, cell death, and the vascular supply (angiogenesis) that provides oxygen and other nutrients to growing tumors.

It is biologically plausible that NDMA acts as a tumor promoter via cell proliferation, cell death, and the angiogenesis (vascular supply of nutrients) -key characteristic #10.

As a result, NDMA is a potent and very toxic carcinogen which exhibits 9 out of the 10 key characteristics of carcinogens. Given the indisputable compelling scientific evidence of carcinogenic activity in animals, evidence in human cell and tissue, substantial evidence of genotoxicity, and considerable knowledge on the many biologically plausible mechanisms of carcinogenicity of NDMA, ***NDMA can clearly cause cancer in animals and humans.***

**ANIMAL STUDIES SUPPORT THAT NDMA IS DISTRIBUTED
THROUGHOUT THE MAMMALIAN BODY**

Studies in animals exposed to NDMA intravenously or orally, confirm its distribution in the fluids of all tissues in the body of mammals. NDMA is miscible in water. Non-ionized molecules of low molecular weight that are soluble in water, such as NDMA tend to move freely across biological membranes and be distributed in the body fluids or in highly vascularized organs and tissues and in the extravascular fluid.

In the patas monkey, NDMA causes DNA damage to a wide spectrum of tissues, with ***at least eight tissues*** sustaining DNA damage including the liver, esophagus, stomach, pancreas, small and large bowel, bladder, prostate, lung, kidney. uterus, ovaries and white blood cells. Thus,

formation, 23 months) in 5 of 11 macaque monkeys including metastases to the lung⁵⁰. Thus, NDEA induces cancer in both rodents and primates, as well as all other species studied.

NDEA is a Mutagen and Carcinogen

A **carcinogen** is a substance that causes cancer. Carcinogens are classified according to their mode of action as genotoxic or nongenotoxic carcinogens. A **mutagen** is a substance that causes mutations. A **mutation** is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer. Compounds that predispose cells to develop tumors, either by direct genotoxicity, or through indirect, non-genotoxic pathways, are called initiators and the normally non-DNA reactive compounds that stimulate tumor development are called promoters²¹. Approximately 70% of known mutagens are also carcinogens or cancer-causing compounds³⁸¹. A compound that acts as both an initiator and a promoter is referred to as a '**complete carcinogen**' because tumor development can occur without the application of another compound, i.e., a promoter³⁸². NDEA, like NDMA, is a complete carcinogen.

The Ten Key Characteristics of Carcinogens: NDEA

As explained previously for NDMA, there are 10 key characteristics of human carcinogens that provide the basis for an objective approach to identifying and categorizing cancer mechanisms when assessing whether a chemical is a potential human carcinogen^{24,25}. Since the properties of each key characteristic have been detailed in the discussion on NDMA, they will not be repeated here for NDEA as the characteristics are the same.

This systematic approach assists in evaluating chemicals and pharmaceutical agents as potential human carcinogens, especially in the absence of convincing epidemiological data on many human cancers²⁴. The key characteristics of carcinogens described by Smith et al. (2016)^{24,25} which are utilized by **IARC** are as follows:

1. Can the agent act as an electrophilic or can be metabolically activated to an electrophile?
2. Is the agent genotoxic?
3. Does the agent alter DNA repair or causes genomic instability?
4. Does the agent induce epigenetic alterations?
5. Does the agent induces oxidative stress?
6. Does the agent induce chronic inflammation?
7. Is the agent immunosuppressive?
8. Does the agent modulate receptor-mediated effects?
9. Does the agent cause immortalization?
10. Does the agent alter cell proliferation, cell death, or nutrient supply?

The first four characteristics focus on the genotoxic nature of the chemical agent. The last six characteristics focus on the non-genotoxic mechanisms in the tumor microenvironment. These 10 key characteristics of human carcinogens are a roadmap for understanding cancer mechanisms when asking whether a chemical or agent is a potential human carcinogen²⁴.

Similar to my analysis of NDMA, I used these key characteristics to determine the bio plausibility of the mechanisms of action for NDEA-induced carcinogenesis. The range of evidence available to determine whether NDEA exhibits these 10 key characteristics includes the following: animal cancer bioassays, studies of specific biological mechanisms in tissues and cells derived from humans, studies of specific biological mechanisms in tissues and cells derived from animals. I only found one study of exposure to humans in which the amount of NDEA was quantified in the diet. As with NDMA, it would be unethical to perform any human trials with NDEA because it is a human carcinogen.

As a demonstration of its potency, NDEA exhibits 9 of 10 key characteristics of human carcinogens. Following each heading, I have listed those studies that are relevant to NDEA for each key characteristic.

Key characteristic #1 – NDEA is metabolically activated to electrophiles via the formation of DNA adducts.

Similar to NDMA, NDEA is metabolically activated before it causes its potent cancer causing activity²⁰². The rate of metabolism of NDEA by slices of organs from rats and hamsters *in vitro* has been measured, and a correlation has been made between the degree of metabolism and the distribution of NDEA-induced tumors^{125,202}. Metabolic activation of NDEA results in the formation of DNA adducts which react with the DNA as part of the cancer initiation process. Metabolic activation of NDEA forms reactive metabolites resulting in ethylation of liver RNA and DNA to form 7-ethylguanine.

NDEA is activated to electrophiles that react in DNA³⁸³. An electrophile (“electron loving”) is a molecule that accepts electrons to form a bond with its reaction partner. Electrophiles rapidly bind to tissues and can lead to cancer; the electrophilic reactivity correlates with the cancer-causing potency of carcinogens such as NDEA and NDMA. NDEA causes cancer because in the human body it triggers potent electrophilic alkylating agents such as DNA adducts¹⁰⁷. These cancer promoting substances are formed by metabolic activation. These electrophiles react with the DNA of target tissue to form altered bases which leads to the initiation of cancer¹⁰⁷.

Similar to NDMA, NDEA is activated by cytochrome P450 enzymes. Metabolic biotransformation of NDEA by cytochrome P450 enzymes produces DNA adducts such as O6-ethyldeoxyguanosine as well as O4- and O6-ethyldeoxythymidine, and active ethyl radical

metabolites that initiate carcinogenesis³⁸³. Similar to NDMA, NDEA-induced DNA adducts, which if not repaired, can lead to cancer formation³⁸⁴. Once bioactivated, NDEA can attack all four DNA bases at positions with high electron density²⁰². This NDEA-induced alkylation attack in each organ reflects the local level of bioactivation capacity, since the diazonium ion is too reactive to be transported to other organs in significant amounts.

It is shown that NDEA forms ethyl adducts at many DNA positions³⁸⁵. Ethyl adducts at thymine 04 are both persistent and mutagenic²⁰². Ethyl-DNA adducts are formed after *in vivo* exposure to NDEA and their persistence contributes to tumor induction. Since this is a relatively simple and rapid alkylation mechanism, NDEA may produce DNA adducts in *any* tissue with appropriate activating cytochrome P450 enzymes.

NDEA-induced metabolic activation has been demonstrated *in vitro* (outside the body) and *in vivo* (inside the body). This NDEA metabolic activation correlates with the induction of NDEA-induced tumors. After administration of NDEA to rats or hamsters, several ethylated DNA adducts were generated in the liver and kidney DNA. These included 7-ethylguanine, O6 ethylguanine, and 3-ethyladenine^{116,386}. In addition to DNA adducts, there is a correlation between carbon dioxide (CO₂), another tumor promoting metabolite produced from NDEA, in the liver, lung and the organ distribution of NDEA-induced tumors as observed *in vivo*³⁸⁷.

Both NDEA and NDMA cause cancer in tissues remote from the site of administration¹⁰⁷. The first bioactivation step for NDEA- DNA adduct formation in rat liver involves o-hydroxylation of NDEA by CYP2E1 and other P450 isozymes leading to the reactive ethyl diazonium ion²⁰². The metabolic activation of NDEA can be mediated by CYP2A6, followed by CYP2E1³⁸⁸. NDEA is hydroxylated by CYP2E1 in the liver and other cytochrome P450 enzymes expressed throughout the human body in various tissues and cells. For example, this was demonstrated in scientific

studies as NDEA activation in rats could be prevented by administration of the cytochrome P450 oxidation inhibitors^{358,389}, supporting that NDEA-induced metabolic activation is mediated via cytochrome P450 enzymes.

Studies of NDEA bioactivation and DNA adduct formation have provided important information for understanding species-to-species extrapolation of NDEA and other DNA-reactive rodent carcinogens and their human relevance²⁰². Methylation of DNA adducts such as O6 position of guanine is one of the chemical events that initiates cancer^{390,391}. In studies where NDEA caused cancer in 100% of animals, the highest concentration of the DNA adduct O6-ethyldeoxyguanosine was detectable in the DNA of cells at the earliest time point examined after only 2 days of NDEA treatment³⁹².

Importantly, NDEA can cause cancer at target organs distant to the site of exposure as these bioactivation pathways are present in any of the cells or tissue that express the enzymes that activate NDEA. Humans express cytochrome P450 enzymes (e.g. CYP2E1) similar to rodents and this P450 enzyme is involved in NDEA activation in animals and humans²⁰². Significantly, as in NDMA, the metabolism of NDEA is similar in humans and rodents. CYP2A6 is an isozyme that is important in tumor formation in other species (and may be more prominent) for the bioactivation of NDEA in humans. Based upon the general similarity of NDEA bioactivation and cancer causing activity among species (e.g. including primate monkeys), NDEA will act as a human carcinogen²⁰².

Another enzyme, CYP2A6, is important in human and mice NDEA bioactivation³⁹³. Cytochrome P450s, including CYP2E1, are important in the initial NDEA bioactivation step in the liver by demonstrating inhibition by various agents. One of the important human bioactivating enzymes, CYP2E1, shares 75% of the nucleotides with rat CYP2E1³⁹⁴. After NDEA is bioactivated to an electrophilic ethyldiazonium ion, it undergoes reactions with nucleophiles, including DNA

bases, to form adducts. The bioactivation is effected by several P450 isozymes including CYP2E1²⁰².

It was found that tumor formation in rat liver was proportional to O4 ethyldeoxythymidine formation in DNA, which is proportional to NDEA dose²⁰². Yamazaki et al. found that human liver microsomes can bioactivate NDEA²⁶³. Cytochrome P450 isozymes other than CYP2E1 are responsible for esophageal activation of NDEA⁶³. In fact, the rat esophagus contains CYP2A3 and/or CYP2A6 and an additional unidentified enzyme that can bioactivate NDEA^{395,396}. NDEA is degraded by the action of the cytochrome P450-dependent monooxygenase system to form its active ethyl radicals²⁰². Different cytochrome P450-dependent monooxygenases, including CYP2A and CYP2B groups and CYP2E1, are considered to be key enzymes involved in the activation of NDEA. Aitio et al. (1991) found individual NDEA bioactivation differences within a group of Wistar rats, measured by N-demethylase activity, which correlated with the NDEA-induced tumorigenic response³⁹⁷. The studies have shown that NDEA triggered tumors in every animal species and strain investigated and that NDEA activation can occur in any tissue, organ, or cell which expresses the cytochrome P450³⁹⁸.

As cited above, there is overwhelming evidence that NDEA is metabolically activated via the formation of DNA adducts to cause cancer. The formation of DNA adducts such as O6-ethyldeoxyguanosine as well as O4- and O6-ethyldeoxythymidine, and active ethyl radical metabolites that initiate carcinogenesis is critical to the cancer-causing activity of NDEA. DNA adducts are metabolically activated to electrophiles to exert NDEA's cancer-causing activity. Due to the compelling evidence in the animal assays, animal *in vitro* and human tissue, it is my opinion that NDEA is a human carcinogen via key characteristic #1.

Thus, it is biologically plausible that NDEA causes cancer via key characteristic #1.

Key characteristic #2: NDEA is Genotoxic.

Similar to NDMA, NDEA is genotoxic and mutagenic³⁹⁹⁻⁴⁰². In contrast, few non-carcinogens are mutagenic³⁹⁹. NDEA is shown to trigger a genotoxic response⁴⁰³. The term “genotoxic” refers to a chemical that causes DNA damage, alteration to the genome (mutation), or both⁴⁰⁴. NDEA is genotoxic as it causes DNA damage (e.g., Comets) in all cell types tested including hepatocytes, blood lymphocytes and bone-marrow cells as shown in the Comet assay reflected by increased tail length⁴⁰⁵. The Comet assay is a sensitive and rapid technique for quantifying and analyzing DNA damage in individual cells. DNA fragmentation is a marker for genotoxic effects, and is confirmed by the micronucleus assay and chromosomal aberration counts⁴⁰⁶. NDEA causes genomic damage in exposed cells. As a consequence, the damaged cells may be triggered to proliferate, leading to the formation of cancerous cells that showed increased cell proliferation, angiogenesis, invasion and metastasis. NDEA causes a significant increase in micronucleus induction and DNA fragmentation⁴⁰⁶.

DNA damage induced by NDEA was demonstrated in nasal, oropharyngeal and laryngeal mucosal cells, but also in peripheral lymphocytes⁴⁰⁷. NDEA induces single-strand DNA breaks⁴⁰⁸, which is a clear form of DNA damage. DNA migration in lymphocytes of patients with cancer, as assessed by the Comet assay, was elevated after exposure of lymphocytes to NDEA⁴⁰⁹. These studies show that NDEA can initiate cancer via genotoxic effects.

DNA damage induced by NDEA increases micronuclei due to DNA breakage which could not be repaired, leading to an increase in chromosomal aberrations and apoptotic cell death which can lead to cancer^{186,406}. Compared to the normal tissue DNA, NDEA-induced tumors exhibited significant formation of random DNA fragments⁴¹⁰. Genotoxicity studies with NDEA were

positive for chromosomal aberrations in rat liver cells⁴¹¹ and NDEA-induced DNA single-strand breaks were found in tumor cells (e.g. hepatoma cell lines).

A mutation is a change in the DNA sequence and usually results from the cell attempting to repair the DNA damage²⁴. Gene or point mutations are changes in nucleotide sequence within a gene²⁴. All of these types of DNA damage may give rise to permanent changes in the nucleotide sequence (mutation) as the cell attempts to repair the damage. The DNA adducts (described in key characteristic #1) formed by NDEA (and NDMA), can lead to mutations unless the DNA damage is repaired⁴¹².

Mutagenicity tests are used to indicate potential carcinogenesis risks³⁸³. NDEA is known to be mutagenic at low concentrations³⁸³. NDEA exhibited mutagenic activity with a positive Ames test and a positive SOS chromotest assay^{413,414}. The Ames test is a widely employed biological assay using bacteria to test whether a given chemical causes mutations in the DNA of the test organism. A positive Ames test indicates that NDEA is mutagenic and can act as a carcinogen because cancer is linked to mutations. The Ames test is a quick and convenient test to estimate the carcinogenic potential of a compound as standard carcinogen assays on rodents (e.g., mice and rats) are time-consuming (taking two to three years to complete) and are expensive. The SOS chromotest is an assay that also tests for the genotoxic potential of chemical compounds. This test was developed as a complement or alternative to the traditional Ames test, which involves growing bacteria on agar plates and comparing natural mutation rates to mutation rates of bacteria exposed to potentially mutagenic chemical. Both the Ames assay and the SOS chromotest are standard, useful tools to screen genotoxic and mutagenic chemicals that can cause cancer in humans.

NDEA is mutagenic in the above tests for bacteria *S. typhimurium*, *E. coli*, and *Neurospora crassa*, and produced mitotic recombination in *S. cerevisiae*, recessive lethal mutations in *D. melanogaster*, and chromosomal aberrations in mammalian cells. Positive responses in bacterial cells required a mammalian metabolic system (Montesano and Bartsch, 1976). Yamazaki et al. also obtained a positive genotoxic response by NDEA with *Salmonella typhimurium* NM2009 using human and rat liver microsomal activation systems⁴¹⁵. In the presence of a rat liver microsomal system *in vitro*, NDEA induced chromosomal aberrations and sister chromatid exchanges in Chinese hamster cells⁴¹⁶. NDEA is mutagenic causing forward mutations and reverse mutations³⁸⁷. For these reasons, NDEA is positive in standard genotoxicity and mutagenic tests.

NDEA also causes breaks in chromosomes (“clastogenic”) as severe clastogenicity (> 50% of cells examined showing aberrations) was observed for NDEA⁴¹⁷. Mutations after NDEA exposure were found at high frequency in the K-ras oncogene of lung tumors in mice⁴¹⁸. NDEA is mutagenic as it is a potent inducer of gene mutations and micronuclei. The genotoxic and mutagenic activity of NDEA is neutralized by inhibitors of various cytochrome P450 (including CYP2E1), suggesting that CYP2E1 can mediate the genotoxic and mutagenic activity of NDEA⁴¹⁹. This supports that NDEA is actively genotoxic and mutagenic, except in scientific studies containing cytochrome P450 inhibitors.

DNA fragmentation is a marker for genotoxic effects, confirmed by the micronucleus assay⁴⁰⁶. NDEA increased the number of micronucleus cells⁴⁰⁶ and caused a significant increase in micronucleus induction and DNA fragmentation⁴⁰⁶. That NDEA increases the level of fragmented DNA in the liver of NDEA-treated rats shows the genotoxic activity of NDEA which can lead to initiation of carcinogenesis⁴²⁰. Any agent capable of reacting with DNA to chemically modify it can cause cancer⁴¹³. NDEA also generates 8-hydroxyguanine⁴²¹ (8-OHG), an indicator

of oxidative damage to DNA, which stimulates oxidative stress (key characteristic #5). Accordingly, the key characteristics of carcinogens often synergize with each other to result in NDEA- and NDMA-induced cancers.

The genotoxicity of NDEA is well established. Given the evidence of genotoxicity, it is my opinion that NDEA causes cancer in humans, as well as other species, due to its genotoxic effects via key characteristic #2.

Thus, it is biologically plausible that NDEA causes cancer via key characteristic #2.

Key characteristic #3: NDEA alters DNA repair and causes genomic instability for agents that inhibit DNA repair

Since tumor initiation can be caused by the replication of an unrepaired DNA lesion, DNA repair enzymes have an important role in preventing cancer¹⁰⁷. Several chemical and physical agents have been shown to inhibit DNA repair and/or activate error-prone DNA repair pathways leading to genomic instability and cancer. Carcinogens can act not only by producing DNA damage *directly*, but also by altering the processes that *control* normal DNA replication or repair of DNA damage²⁴. Accordingly, DNA repair activity is a useful human biomarker for mutagenic agents. Genomic instability is a hallmark of cancer and mutations in DNA repair genes provide the basis for the genomic instability⁴²². The biological processes indicating genomic instability include chromosome aberrations, gene mutations, microsatellite instability, and apoptosis²⁴. In addition, genomic instability can be induced by chronic inflammation (key characteristic #6) independently of DNA damage²⁵.

The ability of the tissue to repair DNA adducts play an important role in the mechanism of NDEA causing cancer. Importantly, NDEA alters DNA replications and promote subsequent DNA damage, thereby priming cells for carcinogenesis. NDEA alters DNA repair which can lead to

genomic instability by increasing the micronucleus induction close to the mitotic index, revealing that DNA repair is inactivated⁴⁰⁶.

The DNA damage induced by NDEA corresponds to an increase in micronuclei due to DNA breakage that cannot be repaired, leading to an increase in chromosomal aberrations, and an increase in apoptotic dead cells (key characteristic #10)⁴⁰⁶. When cells (e.g., hepatocytes) were incubated with NDEA, DNA repair was inactive⁴⁰⁶. Studies show NDEA disrupted DNA/replication leading to cancer (e.g. liver)²²⁷ and that NDEA altered (DNA) repair/replication³²⁵. NDEA provoked a significant increase in micronucleus induction and DNA fragmentation which came close to the mitotic index, again revealing that DNA repair is inactivated⁴⁰⁶.

In summary, NDEA alters the processes that control normal DNA replication or repair of DNA damage. Thus, NDEA induces genomic instability with an increased risk for DNA mutations and other genetic changes during cell division. For these reasons, it is my opinion that NDEA is a human carcinogen via alterations in DNA repair capacity and genomic instability.

Thus, it is biologically plausible that NDEA causes cancer via key characteristic #3.

Key characteristic #4: NDEA induces epigenetic alterations (e.g., DNA methylation)

The term “epigenetic” refers to stable changes in gene expression (e.g., DNA methylation) and chromatin organization that are not caused by changes in the DNA. Many carcinogens alter DNA methylation status via epigenetic changes. Epigenetics is the study on how the environment can cause changes in the way our genes work. Unlike genetic changes, epigenetic changes are reversible and do not change your DNA sequence, but they can change how your body reads a DNA sequence. DNA methylation is common epigenetic signaling tool that cells in the body use

to lock genes in an “off” position. DNA methylation is an important process to preserve normal DNA and chromosome functions, so an error in methylation can lead to cancer.

Both NDEA and NDMA induced DNA methylation (e.g. O6-etG) in animals compared to animals treated with a single dose of NDEA or NDMA alone⁴²³. NDEA also induced epigenetic alterations in a study of liver histone profiles in NDEA-induced foci, dysplastic and neoplastic nodules and stages of cancer (e.g., liver) in experimental rats⁴²⁴. A histone is a protein that provides structural support to a chromosome. NDEA caused high expression of the major histone H2A variant H2A.1 during the process of carcinogenesis⁴²⁴. These studies on the role of NDEA in altering specific histone variant support NDEA-induced cancer via epigenetic changes⁴²⁴. Thus, NDEA can act as a human carcinogen via epigenetic alterations.

As NDEA can disrupt epigenetic mechanisms as a carcinogen in humans and animals via DNA methylation. This epigenetic disruption lends further evidence to my opinion that NDEA can cause cancer via key characteristic #4.

Thus, it is biologically plausible that NDEA causes cancer via key characteristic #4.

Key characteristic #5: NDEA induces oxidative stress and subsequent cellular injury

Oxidative stress is a critical tumor promoting mechanism and can lead to oxidative damage to DNA¹⁶⁵. NDEA triggers oxidative stress as even a single dose of NDEA stimulates oxidative stress within 48 hours⁴²⁵. A single dose of NDEA stimulated levels of oxidative stress markers such as hepatic lipid peroxidation (LPO) and conjugated dienes in the rats⁴²⁶. NDEA-stimulated reactive oxygen species (ROS) results in oxidative stress markers in DNA, proteins, and lipids leading to carcinogenicity and mutagenicity^{341,427}.

Oxidative stress results from an imbalance between molecules that stimulate oxidative stress such as reactive oxygen species (ROS) and their elimination by protective mechanisms.

Increased oxidative stress can promote chronic inflammation and cancer. NDEA-derived reactive oxygen species stimulate chronic inflammation (key characteristic #6) via oxidative stress.

Reactive oxygen species, which can arise from inflammation, can contribute to genomic instability and along with other free radical species play key roles in many of the processes identified as being necessary for the conversion of normal cells to cancer cells^{13,23}. NDEA stimulates the release of pro-inflammatory molecules (e.g. cytokines and nitric oxide) from blood cells activated lead to oxidative stress via pro-inflammatory pathways⁴²⁸. NDEA causes oxidative stress via reactive oxygen species (ROS) via cytochrome P450s (e.g., CYP2E1)⁴²⁹. These reactive oxygen species (ROS) causing oxidative stress damage by NDEA is toxic to the cells leading to tumor promotion^{426,429}.

Importantly, NDEA also reduces anti-oxidative stress markers (antioxidants) such as glutathione reductase (GSH-R) activity as well as total glutathione (GSH) content in the rat liver⁴²⁶. The first line of defense to protect from oxidative stress is to block reactive oxygen species via antioxidants that prevent or reduce oxidative stress. Cells have evolved a series of antioxidant systems to handle these dangerous natural by-products including superoxide dismutases (SODs). Oxidative damage to molecules such as DNA, proteins, and lipids arising from redox imbalances, is normally defended against by enzymes that block oxidative stress (SOD, CAT, GSH-Px, GSH-Red, and Glc 6-PD)⁴²⁰.

The reactive metabolites of NDEA and the free radicals generated by cytochrome P450-dependent enzymes produce oxidative stress, which can lead to cancer³⁴⁵. Lipid peroxidation can result in the formation of several byproducts of oxidative stress, such as malondialdehyde (MDA) and 4-hydroxynonenal. These oxidative stress molecules can attack cells including DNA, thereby

promoting mutagenicity and carcinogenicity⁴³⁰. NDEA causes a reduction in ROS detoxifying enzymes (SOD, CAT, GSH-Px, GSH-Red, and Glc 6-PD) resulting in excessive generation of ROS^{348,420}. Thus, these NDEA-induced reductions could lead to oxidative stress resulting in tumor promotion.

NDEA stimulates oxidative stress in lipids via an increase in the levels of lipid peroxidation products (conjugated dienes, lipid hydroperoxides, and malondialdehydes)⁴²⁰. This key characteristic of carcinogens is not specific to cancer and occur in other inflammatory diseases such as stroke, Alzheimer's disease, Parkinson's disease, and diabetes. Thus, oxidative stress is best analyzed in the context of its impact on other key characteristics such as genotoxicity (key characteristic #2) and chronic inflammation (key characteristic #6). NDEA causes oxidative stress and cellular injury via free radicals^{383,431}. NDEA is so potent in generating oxidative stress including reactive oxygen species it is used as a gold-standard to evaluate detoxification and ROS scavenger drugs or reagents that may prevent oxidative stress such as medicinal plants⁴²⁰.

NDEA causes oxidative stress, oxidative DNA damage and cellular injury by generating reactive oxygen species (ROS) leading to cancer progression^{341,345,425}. NDEA stimulates the levels of oxidative stress markers like lipid peroxidation (LPO), protein carbonyl (PCC), and glutathione-S-transferase (GST) activity and reduces total glutathione (GSH) content⁴³². NDEA stimulates oxidative stress markers including malondialdehyde, conjugated dienes, lipid hydroperoxides, protein carbonyl, and percentage DNA fragmentation⁴²⁰. Exposure to NDEA resulted in a significant decrease in the level of the antioxidants glutathione such as GSH in the liver of rats when compared to the control⁴²⁰.

NDEA impaired antioxidative defense is reflected by a significant elevation in the level of oxidative stress marker (MDA) and a significant depletion of free radical scavenging antioxidants

(GR, GPx, SOD and GSH)⁴³³. NDEA lowers the antioxidant levels in both liver and serum in animals³⁴¹. NDEA also lowers the antioxidant glutathione (GSH)³⁴⁰. NDEA causes the generation of ROS resulting in oxidative stress and cellular injury¹²⁷.

To maintain cellular health in the human body it is essential to have a reactive oxygen species (ROS) scavenger system that blocks oxidative stress³⁴⁵. Antioxidants have been tested in the NDEA-induced oxidative stress models to study the anti-oxidative protective effects of agents such as Vitamin E, ellagic acid, quercetin, curcumin, apigenin, turmeric and garlic powder. These agents all counteract NDEA-induced oxidative damage by reducing or preventing oxidative stress^{350,351,426,427,434}. NDEA-induced hypoxia also triggers oxidative stress via the production of ROS which further activate HIF-1alpha⁴³⁵. NDEA-induced cancer formation was associated with alterations in the hypoxia related proteins such as HIF-1a and HOX. A significant rise in HIF-1a protein expression followed by a concomitant decrease in HOX in NDEA-treated group increases hypoxia and subsequent tumor angiogenesis (key characteristic #10) and metastasis⁴³⁵. The imbalance between antioxidant defense system and generation of reactive oxygen species leads to oxidative stress. Therefore, investigations were made on the antioxidant status of the experimental animals exposed to NDEA⁴³⁶. Superoxide dismutase (SOD) is an enzyme that incurs prominent defensive mechanism against oxidative stress and it was found that NDEA significantly declines the oxidative stress protection factor (SOD) within 14 days of its treatment.

This decline in NDEA-induced activity leads to the generation of superoxide radicals and further oxidative stress⁴³⁷. NDEA induced oxidative stress by lipid peroxidation (LPO) and protein carbonyl formation³⁶⁵. Oxidative stress-induced DNA damage has been measured by single cell gel electrophoresis (Comet assay)³⁶⁵. The NDEA-induced oxidation of DNA in human cells occurs as a consequence of attack by free radicals when oxygen radicals attack DNA bases and

deoxyribose residues, producing damaged bases and single strand breaks increasing tumor promotion.

As a result, NDEA can promote or cause cancer by stimulating oxidative stress via oxygen radical-induced cellular injury which provides evidence to support my opinion that NDEA can cause cancer in humans via oxidative stress and key characteristic #5.

Thus, it is biologically plausible that NDEA is a human carcinogen via oxidative stress in key characteristic #5.

Key characteristic #6: NDEA induces chronic inflammation

Many experimental studies including from my laboratory have confirmed that inflammation can stimulate or induce tumor initiation, growth, and metastasis^{6-10,13,33,182-186}. Inflammation in the tumor microenvironment is now known as a hallmark of cancer¹⁰¹ and is recognized as a key characteristic of carcinogens^{24,25}.

Chronic inflammation promotes tumor growth and progression⁴³⁸. NDEA increased pro-inflammatory cytokines such as TNF-alpha which can promote tumor growth⁴¹⁰. My laboratory and others have shown that chronic inflammation can initiate and promote various cancers^{11,340}.

NDEA increases tumor markers alpha-feto protein (AFP) via stimulation of the pro-inflammatory cytokines TNF-alpha and IL-6 in the blood³²³. NDEA-stimulated cytokines (i.e., TNF-a and IL-6) play a critical role in stimulating tumor cell proliferation and angiogenesis (key characteristics #10)³²³. NDEA-increased pro-inflammatory cytokines reflect an aggressive inflammatory response which promotes tumor growth. These pro-inflammatory molecules such as cytokines act as growth factors to stimulate proliferation, inflammation, angiogenesis, and transformation of tumor cells. Unresolved inflammation is a driving force behind the development

and acceleration of various cancer types including liver, prostate, pancreatic, lung, blood cancers (e.g., lymphoma and leukemia), colon, and head and neck (e.g., esophageal)^{439,440}.

NDEA stimulates inflammation as determined by histopathologic analysis showing mononuclear inflammatory cells³²³. NDEA stimulates pro-inflammatory cytokines IL-1B, IL-2, IL-6, and IL-10 in the tumor tissue³⁴⁰. In fact, NDEA significantly stimulates by twofold to threefold these pro-inflammatory cytokines in rat hepatic tumor tissue. IL-6 is a key procancer cytokine that stimulates inflammation-associated cancers to promote tumor progression, invasion and metastasis⁴⁴¹.

Histological examination of liver tissue done under light microscope can observe the effect of NDEA promoting inflammation on the cells. For example, the liver tissue from NDEA-treated animals showed increased acute inflammatory cells compared to normal histological appearance of liver cells in animals not exposed to NDEA⁴⁴². On histopathological analysis, NDEA-treated rats exhibit an excess inflammation (e.g., inflammatory cells called neutrophils), necrosis, and excessive collagen in the tissues⁴³⁶. Thus, inflammation such as in the liver is prominent in the NDEA-treated group.⁴³⁶ Time-dependent severity of liver inflammation followed by fibrosis is associated with NDEA-increased liver enzymes (e.g., AST, ALT, ALP, γ GT and bilirubin levels). NDEA upregulates the pro-tumorigenic and pro-inflammatory molecule called NF-kB which results in transcription of genes that contribute to cancer via non-genotoxic mechanisms such as cell proliferation, inflammation, oxidative stress and angiogenesis. NDEA increased expression of NF-kB can stimulate tumor growth by promoting inflammation.

NDEA functions as a tumor promotor by stimulating chronic inflammation. By stimulating inflammation, NDEA can accelerate tumor growth by stimulating other key carcinogen characteristics such as oxidative stress, immunosuppression, angiogenesis, and apoptosis (cell

death)⁴³⁹. Importantly, chronic inflammation can promote genotoxicity, oxidative stress and genomic instability. Because NDEA stimulates all of these key characteristics, inflammation can act synergistically with these other key characteristics to promote many types of cancer.

This evidence adds support to my opinion that NDEA can cause and promote human cancer as a carcinogen.

Thus, it is biologically plausible that NDEA is a human carcinogen via chronic inflammation under key characteristic #6.

Key characteristic #7: NDEA is immunosuppressive

Immunosuppression is important to the mechanism of carcinogenesis since the immune system of the human body normally functions to protect against cancers. Chemicals that cause immunosuppression can cause or stimulate cancer. Carcinogens can cause or promote by suppressing the immune system. For example, NDEA induced severe anemia in the hen's egg⁴⁴³ which results in decreased healthy red blood cells to carry adequate oxygen to the body's tissues. Anemia can adversely affect the immune system. If a carcinogen such as NDEA enters the bone marrow it can induce immunosuppression.

Chronic inflammation also induces immunosuppression via induction of proinflammatory mediators and accumulation/activation of immune suppressor cells¹³. Immunosuppression can result from a pro-inflammatory immune response. NDEA strongly affected cellular immune response pathways²⁸⁴ and when tested on gene expression transcriptomic profiling, it showed increased pathways of pro-inflammatory immune response which can promote cancer²⁸⁴. NDEA influenced pathways involved in the stimulation of proinflammatory cytokines, including the IL-1 and IL-6 signaling pathways²⁸⁴. Cytokine production, especially IL-6, plays an important role in

the induction of the acute phase response and stimulation of the intestinal inflammatory response⁴⁴⁴. NDEA has also been shown to cause poorly differentiated carcinomas in immunosuppressed new-born rats⁴⁴⁵.

Since NDEA can disrupt the normal host immune response, which protects from cancer progression, via tumor-promoting inflammation. The ability of NDEA to be immunosuppressive contributes to the pro-carcinogenic activity of NDEA. NDEA notably causes dysfunction of the immune system, which plays a critical role in carcinogenesis.

Thus, it is biologically plausible that NDEA causes cancer via immunosuppression under key characteristic #7.

Key characteristic #8: Modulates Receptor-Mediated Effects

The carcinogen NDEA receptor-mediated activity has not been characterized. Receptor-mediated effects can occur at the cell surface (through ligand-binding) or intracellularly (via the disruption of signaling cascades or actions on nuclear/cytosolic receptors), all of which can modulate transcriptional changes in the nucleus. Thus, both receptor binding and receptor functional activity of NDEA has not been characterized and it is unknown if NDEA exhibits this characteristic.

Key characteristic #9: Causes immortalization

Cancer cells are immortal, and therefore have limitless replicative potential. In contrast, normal cells have a limited lifespan. Immortalization is associated with stemness, the ability of cells to self-replicate indefinitely and to transform into various cell types. The opposite of immortalization and stemness is cellular senescence, a cellular program in which cells stop

dividing. Chemical carcinogens including tobacco, PCBs and asbestos promote immortalization and inhibit senescence.

Morphological transformation of hamster, mouse, or rat non-cancer cells in models of chemical carcinogenesis are a reliable index of tumorigenic potential or the ability of cells to form progressively growing tumors when injected into an animal^{446,447}.

Transformation does not usually occur when exposing non-cancer cells to noncarcinogens⁴⁴⁷. NDEA causes induced malignant transformation of human epithelial cells to result in transformed cells with a prolonged life span⁴⁴⁵. NDEA was shown to form anchorage independent colonies in soft agar⁴⁴⁵, which is a standard assay to test the transformation of normal cells into cancer cells. The soft agar colony formation assay is a well-established method for characterizing the ability of normal cell in culture (*in vitro*) to change into cancer cells and is considered to be one of the best tests for the ability of a normal cell to transform to a cancer cell⁴⁴⁷. In these studies, NDEA-transformed cells exhibit prolonged life span, aneuploid karyotypes, and form anchorage-independent colonies in soft agar, which are qualities of cancer cells⁴⁴⁵.

NDEA also causes the malignant transformation (altered morphology, extended life span, anchorage independent growth, invasiveness, and tumorigenicity, etc. of normal cells called fibroblasts derived from *human* fetal lung⁴⁴⁸. For this reason, NDEA is an effective carcinogen used in research to induce the malignant transformation of human cells such as fibroblasts into cancer cells⁴⁴⁸ and is utilized to study the mechanisms of carcinogenesis²⁰².

NDEA exposure also caused the transformation of anchorage-independent cells by DNA synthesis in a fetal *human* tracheal epithelial cell line⁴⁴⁹. NDEA stimulated the frequency of anchorage-independent colonies grown in soft agar which was directly related to the dose of NDEA⁴⁴⁹. Colony-forming efficiency, as an expression of the cell transformation effect, was also

dependent on the dose of NDEA⁴⁴⁹. NDEA was found to transform normal guinea pig fetal cells in culture⁴⁴⁷. NDEA increased also oxidative stress levels (key characteristic #5) of SOD and CAT enzymes contribute to cancer transformation from normal cells³⁴⁰.

A high profile publication of a study in the high impact journal Nature created a bioassay system that was modified by intraperitoneal injection of NDEA into pregnant hamsters on day 12 of gestation followed by removal of the embryos on day 14, a period that allowed for completion of metabolic interaction⁴⁴⁶. These transformed cells were produced at a much higher frequency than in control cultures from untreated embryos, and they produced tumors (fibrosarcomas) when injected back into animals⁴⁴⁶.

The immortalization evidence of the effects by NDEA on cells adds evidence to support my opinion that NDEA can act as a human carcinogen by stimulating immortalization.

It is biologically plausible that NDEA causes cancer via immortalization under key characteristic #9.

Key characteristic #10: NDEA alters cell proliferation, cell death, or nutrient supply (e.g., angiogenesis)

Sustained cellular proliferation is a key factor in cancer progression. As summarized in the United States Environmental Protection Agency guidance assessing risk of cancer from early-life exposures (EPA, 2005), more frequent cell division during development can result in enhanced fixation of mutations because of the reduced time available for repair of DNA lesions, while clonal expansion of a mutated cell produces a larger population of mutant cells²⁵. Cell death releases pro-inflammatory signals into the surrounding tissue microenvironment, resulting in recruitment of inflammatory cells of the immune system that can participate in tumor promotion through their influence on cancer cell proliferation and invasiveness. Angiogenesis, in which new blood vessels

grow into a tumor, is key to providing nutrients to the cancer. Tumor growth requires angiogenesis to grow¹.

NDEA can alter cell proliferation via cell toxicity activity. NDEA induced *uncontrolled* proliferation in the liver of NDEA treated mice which was evident from the high expression of cell-proliferation associated genes (PCNA, Cyclin D1, and p21) when compared to control³⁵⁷. In another study, NDEA stimulated a higher rate of cell proliferation, which was further evident from increased *PCNA* and *Cyclin D1* expression³⁵⁷. NDEA has induced reduced expression of p21, which blocks proliferation to prevent tumor progression³⁵⁷.

Exposures of NDEA-initiated cells to chemicals with tumor-promoting activity can enhance the development of such tumors by enhancing the proliferation of the initiated cells. At higher doses, the cytotoxicity of NDEA can stimulate cell proliferation, which can increase tumorigenicity. The mutagenic effects of NDEA-induced DNA adducts can also stimulate cell proliferation at rates greater than the cells of the surrounding tissues, thereby establishing a collection of altered cells, which can develop into tumors.

Enhanced cell proliferation by carcinogens increases the rate of the development of initiated cells²⁰². Increased cell proliferation, which is measured by increased DNA replication, has been found for normal cells and for altered hepatic foci during chronic NDEA administration²⁰². In Peto et al, NDEA-induced cell proliferation was important to tumorigenesis in the esophagus¹⁹. In rat liver and esophagus, NDEA increased the tumor proliferation rate resulting in hyperplasia and cancer. Altered foci, induced by NDEA, exhibited about a 10-fold increase in the rate of cell proliferation. Within a few days of NDEA exposure, single hepatocytes that were GST-I(+) had a much greater probability of enhanced DNA synthesis than unaltered hepatocytes. After this NDEA-induced DNA damage, the number of phenotypically altered and

labeled cells increased dramatically in relation to unaltered hepatocyte, providing evidence of cell proliferation.

An interval of NDEA-induced cell toxicity was found by Rajewski who exposed male rats to NDEA. NDEA initially reduced liver cell proliferation to 2/3 control rate for 3-5 days. After this period, cell proliferation increased to 2-3 times the control value. This initial depression of DNA synthesis before an eventual cell proliferative increase resulted from NDEA-induced cell damage or death that accumulated before a regenerative response was triggered^{218,450}.

Increased cell proliferation with increasing NDEA dose rate was found by Rajewsky (1972), who measured the fraction of DNA synthesizing rat liver cells as a function of NDEA dose rate continuously orally administered to male BDIX rats⁴⁵¹. A maximum cell proliferation for NDEA exposed rats was 85%.

Dose-response for NDEA-induced liver-cell proliferation was studied by Deal et al. (1989) using 6-week-old male F344 rats exposed to NDEA in drinking water for 1, 4 or 10 weeks. Exposure to NDEA increased cell proliferation by 300% and 400% in all lobes. The minimum dose required for enhanced cell proliferation correlated with the 1 ppm dose in male rat liver, where there was an increase in dose-response at high-dose exposure compared with low-dose exposure⁴⁵². NDEA increases hepatocyte proliferation^{202,323}. Thus, NDEA-initiated cells have much higher cell proliferation rates than the surrounding hepatocytes.

Tumor initiation, progression, and maintenance commonly involve alterations in cell death (e.g., apoptosis). Studies have shown that dysregulation of cell death is an important cause for the cancer formation. Two forms of cell death include apoptosis and necrosis. NDEA stimulates necrotic tissue damage with cell death³⁴⁰. A single dose exposure of NDEA causes massive activation of proapoptotic mechanisms⁴⁵³. NDEA induces cell death including apoptosis and

necrosis⁴⁰⁶. Metabolites generated from the metabolic activation of NDEA can induce DNA damage that is not repaired, thereby resulting in cytotoxicity and subsequent cell death⁴⁰¹. NDEA also stimulated necrotic cell death in liver cancer in mice⁴¹⁰. These necrotic dead cells also recruit inflammatory cells of the immune system to their place.

The immune inflammatory cells can act as tumor promoters since these cells can help in cancer cell proliferations and foster angiogenesis⁴¹⁰. Angiogenesis is the growth of new blood vessels and is important tumor promotion as tumors require nutrients from the blood supply. Many tumors including liver, lung, bladder, colon, prostate, pancreatic, blood, and esophageal, are angiogenesis-dependent¹. Significant elevation in angiogenesis associated with vascular endothelial growth factor (VEGF) and CD31 proteins were observed in NDEA-treated mice compared to the mice that were not exposed to NDEA control group⁴³⁵. VEGF is a potent angiogenesis factor that can stimulate many types of cancer including liver, prostate, bladder, lung, colon, blood, pancreatic, and esophageal cancers¹. CD31 is a marker of angiogenesis cells called endothelial cells in the tumor⁴. NDEA stimulates tumor angiogenesis in the mice as determined by the increased levels of the angiogenesis markers (i.e., VEGF and CD31 at 10 weeks of NDEA treatment)⁴³⁵. NDEA treatment in the mice significantly raised the pro-angiogenic molecules called matrix metalloproteinases (MMPs) including MMP-9 and MMP-2 in comparison with the control⁴³⁵. For a cancer cell to spread or metastasize from the original primary tumor to other organs, it must locally degrade the tissues. The key molecules allowing the breakdown or degradation of the tissue to allow the cancers to spread are called matrix metalloproteinases (MMPs)⁴⁵⁴. Thus, NDEA can act as a tumor promotor by altering these 3 critical processes: cell proliferation, cell death and the vascular supply (angiogenesis).

It is biologically plausible that NDEA acts as a tumor promotor via cell proliferation, cell death and the angiogenesis (vascular supply of nutrients) under key characteristic #10.

Therefore, similar to NDMA, NDEA is a potent carcinogen which exhibits 9 of the 10 key characteristics of carcinogens. Given the compelling scientific evidence of carcinogenic activity in animals, evidence in human cell and tissue, substantial evidence of genotoxicity and knowledge of the many biologically plausible mechanisms of carcinogenicity of NDEA, **NDEA is a human carcinogen.**

NDMA and NDEA are similar nitrosamines

Among the *N*-nitrosodialkylamines, NDMA and NDEA are the structurally simplest and the most prevalent ones⁴⁵⁵. Importantly, both are alkylating that introduce alkyl radicals into biologically active molecules and thereby prevent their proper functioning. Similar to NDMA, NDEA exhibits a *no-threshold* implying that a carcinogenic response for NDEA can occur at any dose¹⁹. The National Library of Medicine, National Center for biotechnology Information describes N-Nitrosodiethylamine (NDEA) as is a synthetic light-sensitive, volatile, clear yellow oil that is soluble in water, lipids, and other organic solvents, and explains that N-Nitrosodiethylamine affects DNA integrity, probably by alkylation, and is used in experimental research to induce liver tumorigenesis. **It is considered to be reasonably anticipated to be a human carcinogen; a nitrosamine derivative with alkylating, carcinogenic, and mutagenic properties**²⁰² (National Library of Medicine, National Center for Biotechnology Information, N-Nitrosodiethylamine. <https://pubchem.ncbi.nlm.nih.gov/compound/5921>).

When this description is compared to that of NDMA, the similarities are readily apparent: N-Nitrosodimethylamine (NDMA) is described a volatile, combustible, yellow, oily liquid nitrosamine with a faint characteristic odor that decomposes when exposed to light and emits toxic

escape and form a growing tumor years after the initial primary tumor is removed via surgery^{540,583-586}.

CONCLUSION

As set forth in my Summary of Expert Opinions based upon the evidence in total, it is my opinion with a reasonable degree of medical and scientific certainty that the exposure to NDMA and/or NDEA in valsartan containing drugs increases the risk of, has caused and can cause future human cancer.

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Exhibit I

Mechanisms of action of *N*-nitroso compounds

MICHAEL C ARCHER

*Department of Medical Biophysics, University of Toronto, Ontario Cancer Institute,
500 Sherbourne Street, Toronto, Canada M4X 1K9*

I Bioactivation of *N*-nitroso compounds

II Fate of reactive intermediates

III Evidence for the carcinogenic activity of *N*-nitroso compounds in humans

- 1 Nitrosourea chemotherapy
- 2 Nitrosamine poisonings
- 3 Comparative in vitro metabolism
- 4 Studies with cultured human tissues and cells

Keywords *N*-nitroso compounds, *N*-nitrosamines, metabolic activation, reactive intermediates, DNA alkylation, DNA repair, animal-human extrapolation.

Summary

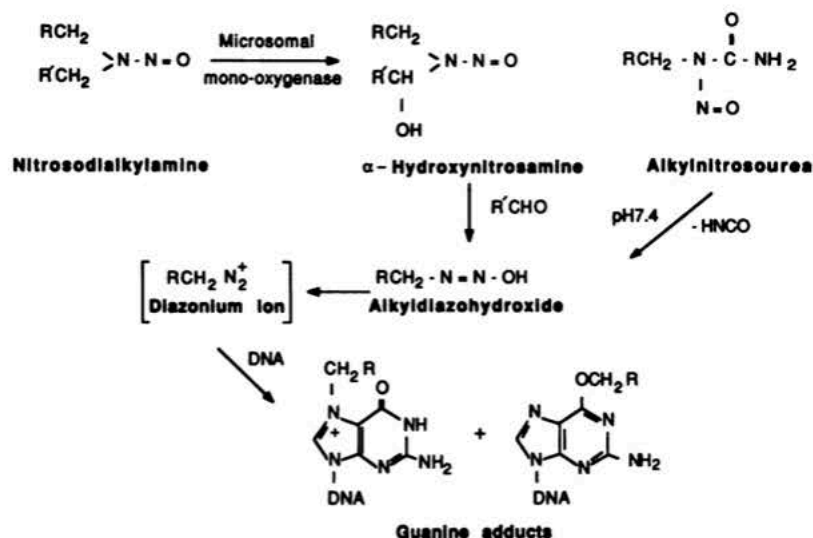
There is ample evidence from studies in experimental animals that *N*-nitroso compounds are carcinogenic because in the body they form potent electrophilic alkylating agents. These reactive intermediates are formed by spontaneous decomposition in the case of nitrosoureas and related compounds, or by metabolic activation in the case of *N*-nitrosamines. The electrophiles subsequently react with DNA of target tissues to form altered bases which leads to the initiation of carcinogenesis. There is now convincing evidence that the biological activity of *N*-nitroso compounds in humans does not differ substantially from that in experimental animals. We can therefore predict with a high degree of confidence that *N*-nitroso compounds including nitrosamines are carcinogenic in man.

I Bioactivation of *N*-nitroso compounds

N-nitrosoureas and related compounds (nitrosamides, nitrosoguanidines, nitrosourethanes, nitrosocyanamides) are chemically reactive, and decompose at physiological pH to form electrophilic alkylating agents as shown in Fig. 1. *N*-nitrosamines, on the other hand, are stable at neutral pH, and require metabolic transformation in vivo in order to exert their carcinogenic effects. This difference explains why nitrosoureas tend to produce tumours at

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Fig. 1 Bioactivation of *N*-nitroso compounds

or near the site of application whereas nitrosamines produce tumours in tissues remote from the site of administration.

Early experiments (reviewed by Magee and Barnes, 1967, and Druckrey *et al.*, 1967) on the pharmacokinetics and in vivo and in vitro metabolism of nitrosamines suggested that these compounds are metabolically activated according to the reaction sequence shown in Fig. 1. Cytochrome P450-dependent hydroxylation at the carbon atom adjacent to the *N*-nitroso group is the critical initial step in the biotransformation. Spontaneous cleavage of the carbon-nitrogen bond in the α -hydroxynitrosamine leads to the production of an aldehyde and the alkyldiazohydroxide. The diazohydroxide finally produces the potent electrophilic alkyl diazonium ion, which may react either with water to form an alcohol or at a nucleophilic site on a biomolecule such as DNA.

Recent experimentation (reviewed by Archer and Labuc, 1985) has substantiated this activation pathway for symmetric and asymmetric nitrosodialkylamines and for cyclic nitrosamines. Metabolic products such as aldehydes, alcohols and molecular nitrogen have been unequivocally identified and quantified for numerous nitrosamines in studies in the whole animal and using cell-free preparations from various organs. Studies of the chemical and biological properties of stable acetoxy derivatives of α -hydroxynitrosamines have provided further support for the activation pathway. Nitrosomethyl(acetoxymethyl)amine was first prepared by Roller *et al.* (1975), who showed that solvolysis of this compound led to the formation of an equimolar mixture of acetic acid, formaldehyde and methanol, as predicted from the activation of nitrosodimethylamine (Fig. 1). Esterases that are ubiquitously

distributed in tissues are responsible for the bioactivation of α -acetoxynitrosamine in vivo. The reactive alkylating agent produced from nitrosomethyl (acetoxymethyl)amine by the action of esterases was shown to yield DNA methylation products identical to those produced by nitrosodimethylamine in rat liver (Kleihues *et al.*, 1979). As expected, nitrosomethyl(acetoxymethyl)amine produces tumours at or near the site of application or in those tissues first exposed to the compound by systemic circulation (eg Habs *et al.*, 1978; Berman *et al.*, 1979), and α -acetoxynitrosamines are potent bacterial mutagens that do not require microsomal activation (eg Camus *et al.*, 1978; Mochizuki *et al.*, 1979). However, the isolation and characterization of free α -hydroxynitrosamines is perhaps the best evidence for the activation mechanism (Mochizuki *et al.*, 1980a).

In addition to α -oxidation, two other metabolic reactions, β -oxidation and ω -oxidation, are involved in the activation of a number of nitrosamines. In 1971, Krüger discovered that in addition to the direct transfer of an intact propyl group to DNA, nitrosodipropylamine also acts as a methylating agent. Indeed, 7-methylguanine is the major alkylation product in hepatic DNA following nitrosodipropylamine administration to rats. The mechanism of this reaction involves two consecutive β -oxidation reactions to yield nitroso-2-oxopropylpropylamine (Fig. 2) (Leung and Archer, 1984). Metabolic α -hydroxylation of this nitrosamine on the propyl side chain with loss of propionaldehyde then forms 2-oxopropyl diazotate. This intermediate undergoes internal cyclization to yield an oxadiazoline which finally breaks down to yield acetic acid and the methylating agent diazomethane. Reactions such as these may also explain the ability of nitrosobis(2-hydroxypropyl)amine, nitroso(2-hydroxypropyl)(2-oxopropyl)amine and nitrosobis(2-oxopropyl)amine to methylate DNA (Lawson *et al.*, 1981; Lijinsky, 1985). These nitrosamines are important because they induce pancreatic tumours, particularly in the Syrian hamster, that are very similar to the pancreatic tumours that are common in humans (reviewed by Pour and Wilson, 1980).

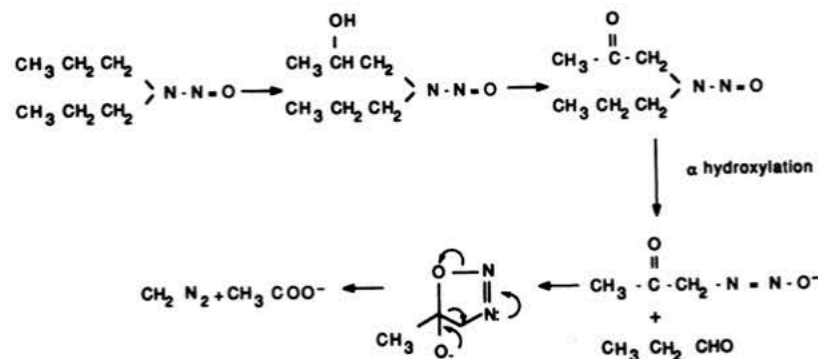


Fig. 2 Mechanism for formation of a methylating agent from nitroso dipropylamine

Nitrosodibutylamine and nitrosobutyl(4-hydroxybutyl)amine, which induce bladder tumours in the rat, have been shown to undergo ω , ω -1 and ω -2, oxidations (reviewed by Okada, 1984). Nitrosobutyl-3-carboxypropylamine is a major urinary metabolite, and probably the proximate carcinogenic form of these nitrosamines. Mochizuki *et al* (1980b) have suggested that the epithelial cells of the bladder activate the nitrosobutyl-3-carboxypropylamine by α -hydroxylation on the 3-carboxypropyl chain, and the resulting α -hydroxynitrosamine is stabilized as the γ -lactone.

Metabolic ω -oxidation reactions followed by β -oxidation have been shown to lead to loss of a two carbon fragment from one side chain of nitrosodibutylamine in a manner analogous to the Knoop mechanism of fatty acid metabolism (Okada, 1984). On the basis of this mechanism, Okada *et al* (1976) proposed that nitrosomethylalkylamines with an even number of carbon atoms would give rise to nitrosomethyl-3-carboxypropylamine, and would be bladder carcinogens, whereas those with an odd number of carbon atoms would not produce the 3-carboxypropyl derivative, and hence would not induce bladder tumours. This prediction has been supported by carcinogenesis studies with a series of nitrosomethylalkylamines (Lijinsky *et al*, 1981).

In addition to metabolic activation reactions, nitrosamines may also be deactivated by metabolism. The best characterized detoxification pathway is denitrosation (Keefer *et al*, 1987 and references therein), although there is some evidence for reduction to corresponding asymmetrical hydrazines (Grilli and Prodi, 1975).

II Fate of reactive intermediates

The electrophilic intermediates produced by chemical decomposition of nitrosoureas and related compounds, or by metabolic activation of nitrosamines, react rapidly with cellular nucleophiles. Attention has focused on reactions with DNA because this is generally considered to be the critical cellular target for carcinogens during tumour initiation.

Although 7-alkylguanine (Fig. 1) (66.8%) is the most abundant modified base in DNA produced by nitrosodialkylamines, a variety of other products have been identified. These include alkylphosphate triesters (12%); 1-, 3- and 7-alkyladenine (0.9%, 2.3%, 0.7%); 3- and O⁶-alkylguanine (Fig. 1) (0.9%, 6.1%); 3-alkylcytosine (0.6%); O⁴-alkylthymine (trace); and unidentified products (10%) (the numbers in parentheses are the relative proportions of the products as a percentage of the total products for methylation of DNA in rat liver by nitrosodimethylamine, reported by O'Connor *et al*, 1979). Not all of these DNA lesions, however, have the same biological importance. Methylation of the 7-position of guanine shows no correlation with carcinogenic activity, but several striking correlations have been obtained between tissue susceptibility to tumour induction and the initial extent of formation and subsequent persistence of O⁶-methylguanine residues (reviewed by Pegg, 1983). There is also some evidence that O⁴-

ethylthymine may be an important lesion for animals continuously exposed to nitrosodiethylamine (Dyroff *et al*, 1986).

Since tumour initiation is probably caused by replication of an unrepaired DNA lesion, DNA repair enzymes undoubtedly have an important role in carcinogenesis. Guanine alkylated at the O⁶ position is repaired in an unusual process in which the alkyl group is actually transferred from the base to a cysteine residue in the repair enzyme (Pegg, 1983). For each base repaired, a molecule of O⁶-alkylguanine-DNA alkyltransferase is irreversibly inactivated by the process. Human cells in culture and human liver generally have a higher capacity to repair O⁶-methylguanine than rodent cells or rodent liver (Montesano and Wild, 1988 and references therein), a factor that may be important in extrapolating from carcinogenesis studies in rodents to humans. Subpopulations of individuals deficient in the ability to repair such DNA lesions, however, may be particularly prone to developing cancer.

The importance of O⁶-alkylguanine in carcinogenesis has been highlighted by recent experiments on the molecular biology of cancer induction by N-nitroso compounds. A high percentage of mammary tumours induced in rats by methyl nitrosourea contained Ha-ras oncogenes which were activated by G to A transitions in the 12th codon (Zarbl *et al*, 1985). This transition has been shown to be caused by O⁶-methylguanine mispairing with thymine during DNA replication (Loechler *et al*, 1984).

III Evidence for the carcinogenic activity of N-nitroso compounds in humans

Although there is no unequivocal evidence for the carcinogenic activity of N-nitroso compounds in humans, a number of different lines of evidence suggest that humans are not resistant to the effects of these compounds.

1 Nitrosourea chemotherapy

Three chloroethylnitrosourea drugs, carmustine/BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea), lomustine/CCNU (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea) and semustine/methyl-CCNU (1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea), have been used for more than a decade to treat patients with malignant melanoma and advanced cancers of the brain, lung and digestive tract. These are antitumour drugs because they are alkylating agents, but this property makes the nitrosoureas carcinogenic. Several recent studies of patients who have undergone cancer chemotherapy have shown that nitrosourea treatment is associated with the subsequent development of acute non-lymphocytic leukaemia and preleukaemia (Boice *et al*, 1983, 1986 and references therein).

2 Nitrosamine poisonings

In 1937, Freund investigated two cases of human poisoning by nitrosodimethylamine caused by industrial exposure. He reported finding toxic parenchymatous hepatitis with ascites. Similar findings in occupationally

exposed workers were reported by Barnes and Magee (1954). More recently, in a case of deliberate poisoning by nitrosodimethylamine in Germany, the victim died of liver decomposition and cirrhosis (Fussganger and Ditschuneit, 1980). The hepatotoxic effects seen in these cases are similar, if not identical, to the acute toxic effects of nitrosodimethylamine seen in rodents (Magee and Barnes, 1967). In a case of poisoning by the same nitrosamine in the United States, Herron and Shank (1980) were able to show the presence of 7-methylguanine and 0⁶-methylguanine in the DNA of a sample of the victim's liver. It is clear, therefore, that humans, like rodents, activate nitrosodimethylamine to a methylating agent.

3 Comparative in vitro metabolism

Several studies have compared the metabolism of nitrosamines or their binding to DNA in human tissue samples and rodents in which the compounds are known to be carcinogenic. Montesano and Magee (1974) compared the metabolism of N-nitrosodimethylamine in liver slices from various species including humans. Measuring CO₂ evolution and 7-methylguanine formation in DNA, they showed that human liver is similar to rat liver in its ability to metabolize nitrosodimethylamine (Table). Liver slices from monkey and trout, which are relatively resistant to the carcinogenic activity of nitrosodimethylamine (Ashley and Halver, 1968; Adamson and Sieber, 1983), possess significantly lower metabolic activities. Microsomes from human liver samples have been shown to metabolize nitrosamines (Lin and Fong, 1980; Yoo *et al.*, 1988). Yoo *et al.* (1988) showed that human liver microsomes are as efficient as rat liver microsomes in the metabolism of nitrosodimethylamine. They also showed that human liver microsomes catalyse the dealkylation and denitrosation of several other nitrosamines. Furthermore, human liver and lung fractions have been shown to convert nitrosamines into metabolites that are mutagenic for bacteria (Czygan *et al.*, 1973; Bartsch *et al.*, 1976; Sabadie *et al.*, 1980).

4 Studies with cultured human tissues and cells

Explant cultures from a variety of different human tissues including bronchus, oesophagus, urinary bladder, colon and pancreatic duct have been used,

Comparative metabolism of N-nitrosodimethylamine in liver tissue slices from various species, including humans

Species	Relative activity ^a
Hamster (Syrian golden)	100
Rat	65
Human	45
Monkey	6.1
Trout	0.1

^a Expressed as percentage of the formation of 7-methylguanine and [¹⁴C] carbon dioxide observed in hamster. Data from Montesano and Magee (1974) adapted by Bartsch and Montesano (1984)

particularly by Harris, Autrup and coworkers (Harris *et al.*, 1982 and references therein) to study nitrosamine metabolism and DNA binding. Nitrosodimethylamine and nitrosodiethylamine were metabolized in all tissues examined, but some tissues were unable to metabolize cyclic and asymmetric dialkyl nitrosamines. There were large quantitative differences in metabolic rates (up to 150-fold) among individuals. In a few instances, DNA methylation by nitrosodimethylamine in human explant cultures has been observed. Furthermore, in vitro transformation of cultures of human pancreatic epithelial cells by nitrosodimethylamine and methylnitrosourea has been reported (Parsa *et al.*, 1981).

In conclusion, the results of these various studies suggest that the biological activity of N-nitroso compounds is similar in humans and experimental animals. It seems unlikely, therefore, that humans will be resistant to the carcinogenic action of these compounds.

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(The author is responsible for the accuracy of the references.)

Environmental exposure to preformed nitroso compounds

ANTHONY R TRICKER, BERTOLD SPIEGELHALDER and ROLF PREUSSMANN

German Cancer Research Center, Institute for Toxicology and Chemotherapy, Im Neuenheimer Feld 280, D-6900 Heidelberg 1, Federal Republic of Germany

I Introduction

II Occupational exposure to nitrosamines

- 1 Factories that produce and use amines
- 2 Leather tanning industry
- 3 Rubber industry
- 4 Metal working industries (machine shops)
- 5 Other industries

III Environmental exposure to preformed nitrosamines

- 1 Cosmetics and toiletries
- 2 Pharmaceutical products
- 3 Agricultural chemicals: pesticides and herbicides
- 4 Rubber products
- 5 Packaging materials
- 6 Air
- 7 Water

IV Conclusions

Keywords: *N*-nitroso compounds, nitrosamine exposure, biological monitoring.

Summary

In the human environment, nitrosatable amine precursors to *N*-nitroso compounds and nitrosating species such as nitrite and oxides of nitrogen are abundant. As a result, the formation of *N*-nitroso compounds and human exposure to these compounds show a rather complex pattern. The largest known human exposures to exogenous *N*-nitrosamines occur in the work place. This is particularly evident in the rubber and tyre manufacturing industry and in metal cutting and grinding shops. Nearly all industries which are concerned with the production and/or use of amines have a related nitrosamine problem. Outside the industrial environment, commodities such as cosmetics, pharmaceuticals, rubber and household products, which are

Exhibit J

[CANCER RESEARCH 40, 3116-3117, September 1980]
0008-5472/80/0040-0000\$02.00

Methylated Purines in Human Liver DNA after Probable Dimethylnitrosamine Poisoning¹

Deborah C. Herron and Ronald C. Shank²

Departments of Community and Environmental Medicine [R. C. S.] and Medical Pharmacology and Therapeutics [D. C. H.], University of California, Irvine, California 92717

ABSTRACT

DNA, isolated from two samples of human liver obtained from a suspected dimethylnitrosamine poisoning, contained 1363 to 1373 μmol of 7-methylguanine per mol of guanine and 273 to 317 μmol of O^6 -methylguanine per mol of guanine. Liver and kidney DNA obtained from unrelated cases contained no detectable methylated purines. From the DNA methylation levels, it is estimated that the dimethylnitrosamine-poisoning victim had been exposed to a dose of 20 mg or more of dimethylnitrosamine per kg of body weight. The results indicate for the first time that humans, like rodents, appear to activate dimethylnitrosamine metabolically to a strong methylating agent, resulting in methylation of liver DNA at both the 7- and O^6 positions of guanine.

INTRODUCTION

The hepatocarcinogenicity of DMN³ has been demonstrated experimentally in 10 animal species (6), yet, in spite of known industrial and laboratory uses, no human cancers have been associated with exposures to this compound. It is now recognized that DMN is widely present in the environment in the food and air supplies and, under appropriate conditions, can form in the human stomach (8). Biochemical evidence suggests that this compound is a strong carcinogen in animals because of its metabolic activation to a highly reactive agent, which methylates target organ DNA at base-pairing sites such as the O^6 position of guanine (6). A recent case in forensic medicine in which 2 victims died of suspected DMN poisoning has now provided *in vivo* evidence that human beings seem to activate this nitrosamine metabolically in the same way, at least qualitatively, as do laboratory animals. Analysis of liver DNA prepared from one of the victims of suspected DMN poisoning indicates the presence of 7-methylguanine and O^6 -methylguanine.

MATERIALS AND METHODS

Twelve frozen samples of human liver, kidney, and heart were received from the Center for Disease Control, Atlanta, Ga. and Poison Lab., Denver, Colo. Tissue analyses were performed without knowledge of the illness or cause of death. The phenolic extraction method of Kirby (4) as modified by Swann and Magee (10) was used to isolate and purify tissue DNA. Nucleic acid could not be isolated from 5 of the samples, which were severely autolyzed. DNA from the remaining 7

tissues was hydrolyzed in 0.1 M HCl (5 mg/ml) for 30 min at 70°, thus releasing all purines as free bases. Chromatographic separation of hydrolysates was carried out using a Partisil-10 strong cation-exchange column (inner diameter, 25 cm \times 4.5 mm; Whatman, Inc., Clifton, N.J.) and 0.06 M ammonium phosphate (pH 2.0) at 2.0 ml/min (3). Elution of fluorescing bases was monitored using a 286-nm excitation wavelength with a 366-nm emission interference filter. Quantitation was achieved using electronic integration calibrated with standard solutions of authentic guanine, 7-methylguanine, and O^6 -methylguanine.

RESULTS AND DISCUSSION

Only 2 DNA samples contained detectable amounts of methylated purines (Table 1). These samples were prepared from 2 liver specimens taken from a 23-year-old male victim of probable DMN poisoning.⁴ The DNA samples from the other tissues were prepared from 2 cases of Reye's syndrome and one case of methyl bromide poisoning; none of these samples contained either 7-methylguanine or O^6 -methylguanine. The amounts of these methylated bases found in the liver from the DMN victim were readily detectable and quantifiable (Chart 1).

This is the first report of the occurrence of O^6 -methylguanine in human liver resulting from DMN exposure. Until recently, methylation of DNA following *in vivo* exposure to DMN was demonstrable only by using radioactively labeled carcinogen or large amounts of tissue, neither of which was available in the human poisoning considered here. The analytical method used in this study achieved high sensitivity by taking advantage of high-pressure liquid chromatography coupled with fluorescence detection (3).

An *in vitro* determination of metabolic activation of [¹⁴C]DMN by rat and human liver slices was reported by Montesano and Magee (7). They found that human liver slices metabolized DMN at a rate such that 0.13% of the DNA guanine was methylated at position 7 in 1 hr compared to 0.17% of the DNA guanine in rat liver slices.

We have attempted to determine whether our data are consistent with an exposure to an acutely toxic dose of DMN. Craddock (1) has determined that a dose of 5 mg of DMN per kg of body weight results in the formation of approximately 1300 μmol of 7-methylguanine per mol of guanine in rat liver DNA 5 hr after administration of carcinogen p.o. If the human metabolizes DMN at only 68% of the rate at which the rat forms the active methylating agent as suggested by the study of Montesano and Magee (7) mentioned above, then the human dose could approximate 5 mg + 0.68 or 7 mg/kg of body weight. Since the victim died 5 days after presumed exposure,

¹ This work was supported by the Environmental Toxicology Laboratories, College of Medicine, University of California, Irvine, Calif.

² To whom requests for reprints should be addressed.

³ The abbreviation used is: DMN, dimethylnitrosamine.

Received January 7, 1980; accepted May 19, 1980.

⁴ R. Kimbrough and S. Cooper, personal communication.

Table 1
Methylated purines in human DNA

DNA source	Cause of death	Methylated purines ($\mu\text{mol}/\text{mol}$ guanine)	
		7-Methyl- guanine	O ⁶ -Methyl- guanine
Liver ^a	DMN poisoning	1363	273
Liver ^a	DMN poisoning	1373	317
Liver	MeBr ^b poisoning	ND ^c	ND
Kidney	MeBr poisoning	ND	ND
Liver ^a	Reye's syndrome	ND	ND
Liver ^a	Reye's syndrome	ND	ND
Liver	Reye's syndrome	ND	ND

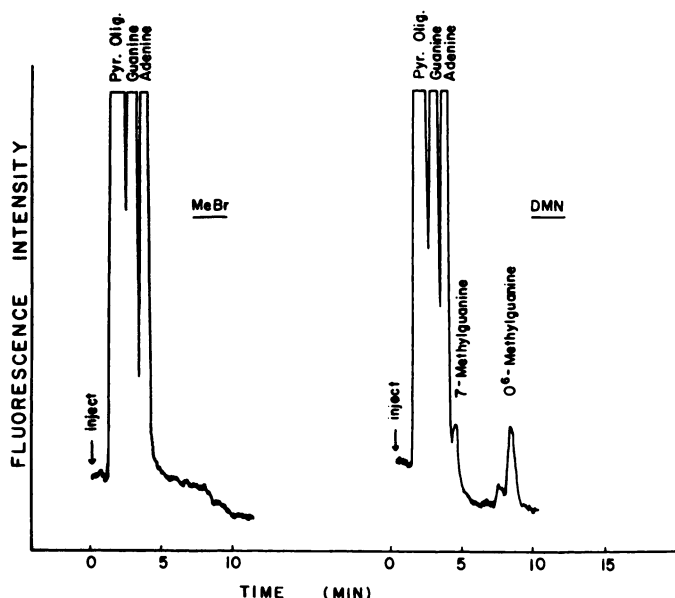
^a Two liver specimens analyzed from one victim.^b MeBr, methyl bromide.^c ND, not detected (limits of detection, 220 μmol 7-methylguanine per mol guanine and 8 μmol O⁶-methylguanine per mol guanine).

Chart 1. Elution profiles of liver DNA hydrolysate from victims of methyl bromide (MeBr) and DMN poisonings. DNA was hydrolyzed and fractionated to separate pyrimidine oligonucleotides (Pyr. Olig.), guanine, adenine, 7-methylguanine, and O⁶-methylguanine by the liquid chromatographic method of Herron and Shank (3). Eluting bases were detected by fluorescence at a 286-nm excitation with a 366-nm emission interference filter. The unlabeled peak eluting before O⁶-methylguanine has not been identified. The amount of 7-methylguanine in the liver of the victim of DMN poisoning is approximately 5 times greater than the amount of O⁶-methylguanine. The eluting peak of O⁶-methylguanine appears greater than that for 7-methylguanine because the relative fluorescence of O⁶-methylguanine:7-methylguanine is 18:1 at a 286-nm excitation. (Redrawn from original.)

and since 7-methylguanine spontaneously depurinates from DNA (half-life, 24 to 48 hr), the human dose probably was considerably greater than 7 mg/kg of body weight. Pegg (9) has shown a dose-dependent relationship between DMN exposure and the O⁶-methylguanine:7-methylguanine ratio in rat liver DNA. This ratio approaches 0.1 at about 20 mg of DMN

per kg of body weight. The ratio in the human liver DNA reported here was 0.2; if extrapolation can be made from rat data, this provides additional evidence that the human exposure was probably greater than 20 mg/kg of body weight. The 50% lethal dose for DMN administered p.o. in the rat is 27 to 41 mg/kg of body weight (2); hence, the finding of the amounts of methylated purines in the human liver DNA reported here is consistent with an exposure to a level of DMN likely to be fatal.

In view of current theories of chemical carcinogenesis, the detection of methylated bases, particularly O⁶-methylguanine, in human tissue after a probable exposure to DMN has important implications. Considerable attention has been focused on the presence and quantitative analysis of alkylated bases in DNA of animals treated with chemical carcinogens. Several attempts have been made to associate levels and sites of DNA alkylation with carcinogenicity. Although quantitatively a minor product, O⁶-methylguanine may be more closely associated with carcinogenicity than the more frequently occurring 7-methylguanine (5). Both rats and humans, then, appear capable of metabolically activating DMN to a strong methylating agent, which interacts with the same sites in liver DNA in both species.

ACKNOWLEDGMENTS

We wish to thank Dr. Renate Kimbrough, Center for Disease Control, Atlanta, Ga. and Mr. Samuel Cooper, Deputy County Attorney, Omaha, Nebr. for supplying the tissue specimens.

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Exhibit K

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the United Nations Environment Programme, the International Labour Organization, or the World Health Organization.

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N-NITROSODIMETHYLAMINE

First draft prepared by

R.G. Liteplo and M.E. Meek, Health Canada, Ottawa, Canada, and

W. Windle, Environment Canada, Ottawa, Canada

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Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organization, and the World Health Organization, and produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals.



World Health Organization
Geneva, 2002

The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

WHO Library Cataloguing-in-Publication Data

N-Nitrosodimethylamine.

(Concise international chemical assessment document ; 38)

1.Dimethylnitrosamine - toxicity 2.Risk assessment 3.Environmental exposure 4.Occupational exposure I.International Programme on Chemical Safety II.Series

ISBN 92 4 153038 3
ISSN 1020-6167

(NLM Classification: QZ 202)

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The Federal Ministry for the Environment, Nature Conservation and Nuclear Safety, Germany, provided financial support for the printing of this publication.

Printed by Wissenschaftliche Verlagsgesellschaft mbH, D-70009 Stuttgart 10

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FOREWORD

Concise International Chemical Assessment Documents (CICADs) are the latest in a family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organization (ILO), and the United Nations Environment Programme (UNEP). CICADs join the Environmental Health Criteria documents (EHCs) as authoritative documents on the risk assessment of chemicals.

International Chemical Safety Cards on the relevant chemical(s) are attached at the end of the CICAD, to provide the reader with concise information on the protection of human health and on emergency action. They are produced in a separate peer-reviewed procedure at IPCS. They may be complemented by information from IPCS Poison Information Monographs (PIM), similarly produced separately from the CICAD process.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are provided as guidance only. The reader is referred to EHC

170¹ for advice on the derivation of health-based guidance values.

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

Procedures

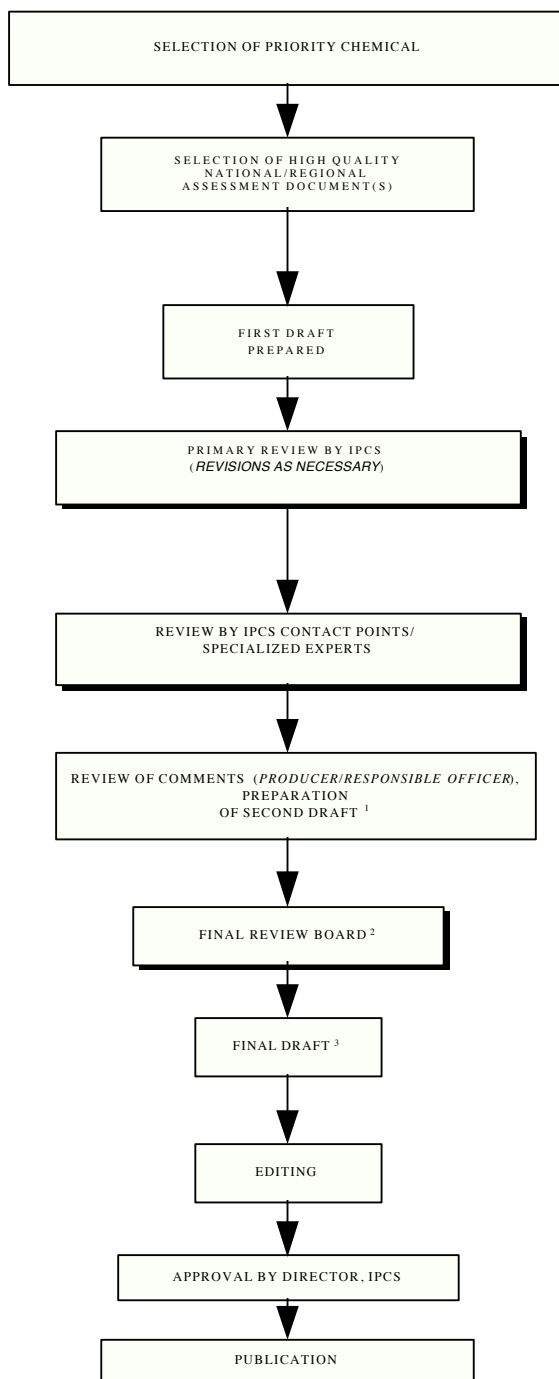
The flow chart on page 2 shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment. The IPCS Risk Assessment Steering Group advises the Co-ordinator, IPCS, on the selection of chemicals for an IPCS risk assessment, the appropriate form of the document (i.e., EHC or CICAD), and which institution bears the responsibility of the document production, as well as on the type and extent of the international peer review.

The first draft is based on an existing national, regional, or international review. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The first draft undergoes primary review by IPCS and one or more experienced authors of criteria documents to ensure that it meets the specified criteria for CICADs.

The draft is then sent to an international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers' comments.

¹ International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits*. Geneva, World Health Organization (Environmental Health Criteria 170).

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CICAD PREPARATION FLOW CHART

¹ Taking into account the comments from reviewers.

² The second draft of documents is submitted to the Final Review Board together with the reviewers' comments.

³ Includes any revisions requested by the Final Review Board.

N-Nitrosodimethylamine

A consultative group may be necessary to advise on specific issues in the risk assessment document.

The CICAD Final Review Board has several important functions:

- to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
- to verify that the peer reviewers' comments have been addressed appropriately;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology or because of their experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

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1. EXECUTIVE SUMMARY

This CICAD on *N*-nitrosodimethylamine (NDMA) was prepared jointly by the Environmental Health Directorate of Health Canada and the Commercial Chemicals Evaluation Branch of Environment Canada based on documentation prepared concurrently as part of the Priority Substances Program under the *Canadian Environmental Protection Act* (CEPA). The objective of assessments on Priority Substances under CEPA is to assess potential effects of indirect exposure in the general environment on human health as well as environmental effects. Although occupational exposure was not addressed in the source document (Environment Canada & Health Canada, 2001), information on this aspect has been included in this CICAD. Data identified as of the end of August 1998 (environmental effects) and August 1999¹ (human health effects) were considered in this review. Other reviews that were also consulted include IARC (1978), ATSDR (1989), OME (1991, 1998), and BIBRA Toxicology International (1997, 1998). Information on the nature of the peer review and availability of the source document is presented in Appendix 1. Information on the peer review of this CICAD is presented in Appendix 2. This CICAD was approved as an international assessment at a meeting of the Final Review Board, held in Geneva, Switzerland, on 8–12 January 2001. Participants at the Final Review Board meeting are listed in Appendix 3. The International Chemical Safety Card for NDMA (ICSC 0525), produced by the International Programme on Chemical Safety (IPCS, 1993), has also been reproduced in this document.

N-Nitrosodimethylamine (NDMA) is the simplest dialkyl nitrosamine. It is no longer used industrially or commercially in Canada or the USA but continues to be released as a by-product and contaminant from various industries and from municipal wastewater treatment plants. Major releases of NDMA have been from the manufacture of pesticides, rubber tires, alkylamines, and dyes. NDMA may also form under natural conditions in air, water, and soil as a result of chemical, photochemical, and biological processes and has been detected in drinking-water and in automobile exhaust.

Photolysis is the major pathway for the removal of NDMA from surface water, air, and land. However, in surface waters with high concentrations of organic substances and suspended matter, photodegradation is much slower. In subsurface water and in soil, biodegradation is the removal pathway of importance. NDMA is unlikely to be transported over long distances in air or to partition to soil and sediments. Because of its solubility and low partition coefficient, NDMA has the potential to leach into and persist in groundwater. It is metabolized and does not bioaccumulate. NDMA is generally not detectable in surface waters, except for localized contamination from industrial sites, where end-of-pipe effluent concentrations as high as 0.266 µg/litre have been measured.

In limited surveys in the country on which the sample risk characterization is based (i.e., Canada), NDMA has not been detected in ambient air, except in the vicinity of industrial sites. Low concentrations of NDMA — formed in water treatment plants or from groundwater contaminated by industrial effluents, for example — have been measured in drinking-water. The presence of NDMA has been demonstrated in some foods, most frequently in beer, cured meat, fish products, and some cheeses, although levels of NDMA have decreased in these products in recent years owing to changes in food processing. Exposure can also result from the use of consumer products that contain NDMA, such as cosmetics and personal care products, products containing rubber, and tobacco products.

Based upon laboratory studies in which tumours have been induced in all species examined at relatively low doses, NDMA is clearly carcinogenic. There is overwhelming evidence that NDMA is mutagenic and clastogenic. While the mechanism by which NDMA induces tumours is not fully elucidated, DNA adducts (in particular, *O*⁶-methylguanine) formed by the methyl-diazonium ion generated during metabolism likely play a critical role. Qualitatively, the metabolism of NDMA appears to be similar in humans and animals; as a result, it is considered highly likely that NDMA is carcinogenic to humans, potentially at relatively low levels of exposure.

Data on non-neoplastic effects in laboratory animals associated with exposure to NDMA are limited, attributable primarily to the focus on its carcinogenicity. Effects on the liver and kidney in repeated-dose toxicity studies, embryo toxicity and embryo lethality in single-dose developmental studies, and a range of immunological effects (suppression of humoral- and cell-mediated immunity) reversible at lowest concentrations have been reported.

¹ New information flagged by the reviewers and in a literature search conducted prior to the Final Review Board meeting has been scoped to indicate its likely impact on the essential conclusions of this assessment, primarily to establish priority for its consideration in an update. More recent information not critical to the hazard characterization or exposure-response analysis, considered by reviewers to add to informational content, has been added.

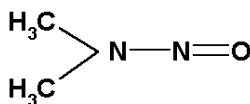
***N*-Nitrosodimethylamine**

Cancer is clearly the critical end-point for quantitation of exposure–response for risk characterization of NDMA. In addition to it being best characterized, in general, tumours occur at lowest concentration, compared with those typically reported to induce non-cancer effects. The lowest tumorigenic dose₀₅ for the development of hepatic tumours in male and female rats exposed to NDMA in the critical study was 34 µg/kg body weight per day for the development of biliary cystadenomas in female animals. This equates to a unit risk of 1.5×10^{-3} per µg/kg body weight. Based on estimated intakes of NDMA in ambient air and contaminated drinking-water (groundwater) in the sample risk characterization, risks in the vicinity of industrial point sources are $>10^{-5}$. Those for ambient drinking-water are between 10^{-7} and 10^{-5} . NDMA is a genotoxic carcinogen, and exposure should be reduced to the extent possible.

Acute and chronic toxicity data are available for aquatic organisms. The toxic effect that occurred at lowest concentration was a reduction in the growth of algae at 4000 µg/litre. In the sample risk characterization, concentrations of NDMA in surface waters in the source country are less than the threshold for adverse effects estimated for aquatic organisms. Data on concentrations of NDMA in sediments or in soil in the sample country were not identified.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

N-Nitrosodimethylamine, or NDMA, is the simplest dialkylnitrosamine, with a molecular formula of C₂H₆N₂O and a relative molecular mass of 74.08 (ATSDR, 1989) (Figure 1). NDMA belongs to a class of chemicals known as *N*-nitroso compounds, characterized by the *N*-nitroso functional group (–N=N=O), and to the family of nitrosamines, which, in addition, possess an amine function (–NR₂, where R is H or an alkyl group). NDMA is also known as dimethylnitrosamine, dimethyl-nitrosoamine, *N,N*-dimethylnitrosamine, *N*-methyl-*N*-nitrosomethanamine, *N*-nitroso-*N,N*-dimethylamine, DMN, and DMNA. NDMA has the Chemical Abstracts



Service (CAS) registry number 62-75-9.

Figure 1: Chemical structure of NDMA.

NDMA is a volatile, combustible, yellow, oily liquid. It is susceptible to photolytic breakdown due to its absorption of ultraviolet light (Sax & Lewis, 1987). The physical/chemical properties relevant to the environmental fate of NDMA and utilized in the modelling of environmental partitioning (section 5.6) are presented in Table 1. Additional properties are presented in the International Chemical Safety Card reproduced in this document.

Table 1: Physical and chemical properties of NDMA.

Physical/chemical property	Value ^a
Melting point (°C)	50
Boiling point (°C)	151–154
Log <i>K</i> _{ow}	0.57
Vapour pressure	1080 Pa (25 °C)
Henry's law constant	3.34 Pa m ³ /mol (25 °C)
Solubility	miscible

^a Includes experimental and calculated values listed in Callahan et al. (1979); Clayton & Clayton (1981); ATSDR (1989); Budavari et al. (1989); OME (1991); DMER & AEL (1996).

The conversion factor for NDMA in air is 1 ppm = 3.08 mg/m³.

3. ANALYTICAL METHODS

Analytical methods for NDMA consist of concentration followed by chromatographic separation of the components in the extract and detection of the *N*-nitrosamine. Concentration steps include liquid–liquid extraction and solid-phase extraction. Chromatographic separations have been achieved almost exclusively by gas chromatography. Detection of NDMA has been accomplished by flame ionization detectors (Nikaido et al., 1977), nitrogen–phosphorus detectors (US EPA, 1984), the Hall electrolytic conductivity detector operated in the reductive mode (von Rappard et al., 1976; US EPA, 1984), the thermal energy analyser or chemiluminescent nitrogen detector (Fine et al., 1975; Fine & Rounbehler, 1976; Webb et al., 1979; Kimoto et al., 1981; Parees & Prescott, 1981; Sen & Seaman, 1981a; Sen et al., 1994; Tomkins et al., 1995; Tomkins & Griest, 1996), and mass spectrometry. NDMA is also analysed by electron ionization low-resolution mass spectrometry (Sen et al., 1994), high-resolution mass spectrometry (Taguchi et al., 1994; Jenkins et al., 1995), chemical ionization tandem mass spectrometry on an ion trap mass spectrometer (Plomley et al., 1994), and laser

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ionization time-of-flight mass spectrometry (Opsal & Reilly, 1986). Liquid chromatography has also been used in conjunction with a photolysis reactor and (electrospray ionization) mass spectrometry (Volmer et al., 1996). Detection limits range from 0.150 µg/litre using nitrogen–phosphorus detectors (US EPA, 1984) to 0.002 µg/litre using a gas chromatograph–thermal energy analyser (Kimoto et al., 1981; Tomkins et al., 1995; Tomkins & Griest, 1996) to 0.001 µg/litre using gas chromatography–high-resolution mass spectrometry (Taguchi et al., 1994; Jenkins et al., 1995). Comparable detection limits are possible with chemical ionization tandem mass spectrometry on an ion trap mass spectrometer (Plomley et al., 1994).

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

Data on sources and emissions from the source country of the national assessment on which the CICAD is based (i.e., Canada) are presented here as an example. Sources and patterns of emissions in other countries are expected to be similar, although quantitative values may vary.

4.1 Natural sources

NDMA can be formed as a result of biological, chemical, or photochemical processes (Ayanaba & Alexander, 1974). It may be present in water, air, and soil due to chemical reaction between ubiquitous, naturally occurring precursors classified as nitrosatable substrates (secondary amines) or nitrosating agents (nitrites) (OME, 1998). For example, NDMA may form in air during nighttime as a result of the atmospheric reaction of dimethylamine (DMA) with nitrogen oxides (Cohen & Bachman, 1978). Soil bacteria may also synthesize NDMA from various precursor substances, such as nitrate, nitrite, and amine compounds (ATSDR, 1989). NDMA precursors are widespread throughout the environment, occurring in plants, fish, algae, urine, and faeces (Ayanaba & Alexander, 1974).

4.2 Anthropogenic sources

NDMA is produced as a by-product of industrial processes that use nitrate and/or nitrites and amines under a range of pH conditions. This is due to inadvertent formation when alkylamines, mainly DMA and trimethylamine, come into contact and react with nitrogen oxides, nitrous acid, or nitrite salts or when trans-nitrosation via nitro or nitroso compounds occurs

(ATSDR, 1989). Therefore, NDMA may be present in discharges of such industries as rubber manufacturing, leather tanning, pesticide manufacturing, food processing, foundries, and dye manufacturing and, as a result, in sewage treatment plant effluent. Almost all of the releases in the source country (i.e., Canada) are to water.

NDMA has also been detected in emissions from diesel vehicle exhaust (Goff et al., 1980).

NDMA may form directly in sewage as a result of the biological and chemical transformation of alkylamines in the presence of nitrate or nitrite (Ayanaba & Alexander, 1974; ATSDR, 1989). It may also be released into the environment as the result of application of sewage sludge to soils rich in nitrate or nitrite.

NDMA may also be formed during the treatment of drinking-water (OME, 1994). NDMA's precursor, DMA, together with nitrite, may enter surface water streams from agricultural runoff (V.Y. Taguchi, personal communication, 1998). Water treatment plants incorporating a chlorination process (e.g., sodium hypochlorite) will produce NDMA from these precursors (Jobb et al., 1993; Graham et al., 1996). Ultraviolet treatment can decompose NDMA to DMA (Jobb et al., 1994). However, it is also possible to generate/regenerate NDMA from the DMA within distribution systems that have post-chlorination (V.Y. Taguchi, personal communication, 1998).

NDMA may be released into the environment as a result of use of certain pesticides contaminated with this compound (Pancholy, 1978). NDMA is present in various technical and commercial pesticides used in agriculture, hospitals, and homes as the result of its formation during the manufacturing process and during storage. The following DMA formulation pesticides may contain NDMA as a microcontaminant: bromacil, benazolin, 2,4-D, dicamba, MCPA, and mecoprop (J. Ballantine, personal communication, 1997; J. Smith, personal communication, 1999).

Since 1990, in testing in Canada of over 100 samples of formulated pesticidal products (DMA salt of phenoxy acid herbicides) potentially contaminated by NDMA, the compound was detected in 49% of the samples, with an average concentration of 0.44 µg/g. Only six samples contained concentrations above 1.0 µg/g, with a range from 1.02 to 2.32 µg/g. Concentrations in pesticides have decreased over time. In 1994, approximately 1 million kilograms of DMA-formulated phenoxy acid herbicides for commercial use were applied to the terrestrial environment in Canada (G. Moore, personal communication, 1999). Based on the average concen

N-Nitrosodimethylamine

tration of NDMA mentioned above and per cent estimate of detection, it was calculated that approximately 200 g of NDMA may have been released into the environment through the use of these herbicides.

4.3 Production and use

There are no industrial or commercial uses of NDMA in Canada or the USA. NDMA was used in Canada in the past and may still be used in other countries in rubber formulations as a fire retardant and in the organic chemical industry as an intermediate, catalyst, antioxidant, additive for lubricants, and softener of copolymers (ATSDR, 1989; Budavari et al., 1989).

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION**5.1 Air**

NDMA has a low vapour pressure (1080 Pa at 25 °C), and, if emitted to or formed in air, it is not likely to adsorb to airborne particulate matter and is expected to exist almost entirely in the vapour phase. In daylight, it degrades rapidly by direct photolysis to form dimethylnitramine. The photolytic half-life of NDMA vapour exposed to sunlight ranges between 0.5 and 1.0 h (Hanst et al., 1977). Half-lives for the reaction with hydroxyl radicals range from 25.4 to 254 h in air (Atkinson, 1985). Modelling of environmental partitioning (section 5.6) is based on a half-life for NDMA in air of 5 h (DMER & AEL, 1996). The short half-lives for NDMA in air suggest that it is not persistent in this compartment.

5.2 Water

Since NDMA is miscible in water and has a low vapour pressure and a low octanol/water partition coefficient ($\log K_{ow}$ of 10.57), it is not likely to bioaccumulate, adsorb to particulates, or volatilize to any significant extent (Thomas, 1982; ATSDR, 1989; OME, 1991). Oxidation, hydrolysis, biotransformation, and biodegradation are not significant factors affecting the fate of NDMA in lake water (Tate & Alexander, 1975). Photodegradation is the main process for removing NDMA from the aquatic environment. The efficiency of removal of NDMA depends on the characteristics of the particular water environment. Typically, photodegradation of NDMA is much slower in waters with high concentrations of organic substances and suspended solids than in clear water bodies. The rate of degradation through photolysis may be significantly decreased in the

presence of interferences with light transmission, such as ice cover on receiving water bodies (Conestoga-Rovers & Associates, 1994; E. McBean, personal communication, 1999). This observation is supported in the groundwater compartment, where, in the absence of light, NDMA has the potential to persist (OME, 1991).

Modelling of environmental partitioning (section 5.6) is based on a mean half-life of 17 h for NDMA in surface water at 25 °C (DMER & AEL, 1996). Howard et al. (1991) reported a half-life range for NDMA in groundwater of 1008–8640 h, based on estimated unacclimated aqueous aerobic biodegradation.

5.3 Sediment

Modelling of environmental partitioning (section 5.6) is based on a mean half-life of 5500 h for NDMA in sediment at 25 °C (DMER & AEL, 1996). Factors that slow degradation include anoxic conditions and lack of illumination, the former by preventing the generation of oxidants and the latter by preventing photolysis and the generation of oxidants by photolytic processes.

5.4 Soil

On soil surfaces, photolysis and volatilization rapidly remove NDMA. Oliver (1979) reported that 30–80% of an unreported concentration of NDMA volatilized from the soil within the first few hours of application to the soil surface. Once incorporated into subsurface soil, however, NDMA will be highly mobile, with the potential to migrate into groundwater supplies. Subsurface biodegradation is slightly slower under anaerobic than under aerobic conditions (ATSDR, 1989). Soil type only slightly affects biodegradation of NDMA. Aeration of soil improved biodegradation compared with waterlogged soil. Pre-exposure of bacteria to NDMA increased biodegradation in soil (Mallik & Tesfai, 1981). Modelling of environmental partitioning (section 5.6) is based on a mean half-life of 1700 h for NDMA in soil at 25 °C (DMER & AEL, 1996).

5.5 Biota

Although NDMA is not present in plants under natural conditions, it can be taken up from the growth medium. Lettuce and spinach plants absorb NDMA from sand, soil, and water after exposure for 2 days to concentrations ranging from 10 to 100 mg NDMA/kg wet weight, with 3.25% and 0.38% being taken up from the growth medium by lettuce and spinach plants, respectively (Dean-Raymond & Alexander, 1976).

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A bioconcentration factor of 0.2 has been estimated for NDMA (Bysshe, 1982). However, conventional estimates of bioconcentration factors (correlation with K_{ow}) are precluded, since, generally, biota can biotransform NDMA (OME, 1998).

5.6 Environmental partitioning

Fugacity modelling provides an overview of key reaction, intercompartment, and advection (movement out of a system) pathways for NDMA and its overall distribution in the environment. A steady-state, non-equilibrium model (Level III fugacity model) was run using the methods developed by Mackay (1991) and Mackay & Paterson (1991). Values for physical/chemical properties utilized in the modelling are presented in Table 1; those for half-lives in various media are presented in sections 5.1–5.4 above. Modelling was based on an assumed default emission rate of 1000 kg/h into a region of 100 000 km², which includes a surface water area (20 m deep) of 10 000 km². The height of the atmosphere was assumed to be 1000 m. Sediments and soils were assumed to have an organic carbon content of 4% and 2% and a depth of 1 cm and 10 cm, respectively. The estimated per cent distribution predicted by this model is not affected by the assumed emission rate.

Modelling predicts that when NDMA is continuously released into a medium, most of it will be present in that medium at steady state. For example, if NDMA is discharged into water, almost all of it will be present in the aqueous phase, with very small amounts in air and soil. Almost all of the NDMA is removed by reaction in water. Similarly, most NDMA released to air will exist in the atmosphere, with very small amounts in soil and water. Finally, when NDMA is discharged continuously to soil, almost all of the substance is transported to surface water, and about a third goes into the atmosphere. However, since NDMA is much more persistent in soil than in water or air at steady state, almost all of the NDMA is present in soil, with very little in surface water, and even less in the atmosphere (DMER & AEL, 1996).

In summary, the Level III fugacity model predicts that if NDMA is emitted into water or air, it will be found in, and react in, the medium of discharge. Emission of NDMA into water or air will tend to result in localized contamination of short duration. If emitted to soil, NDMA moves to the water or air compartments, where it undergoes reaction, or it reacts slowly in the soil. Because rates of volatilization, adsorption, runoff, and reaction in soil are relatively slow compared with reaction in air and water, the persistence of NDMA emitted to soil is longer, and there is potential for NDMA

to move into the groundwater compartment (DMER & AEL, 1996).

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Data primarily on concentrations in the environment from the source country of the national assessment on which the CICAD is based (i.e., Canada) are presented here as a basis for the sample risk characterization. Patterns of exposure in other countries are expected to be similar, although quantitative values may vary.

6.1 Environmental levels

6.1.1 Ambient air

There is little information on the presence or concentrations of NDMA in ambient (i.e., outdoor) air in Canada or elsewhere. Limited Canadian data are restricted to the province of Ontario, where short-term measurements have been taken in the immediate vicinity of potential point sources of discharge to the atmosphere, for comparison with background measurements from other urban locations. No data on airborne concentrations at rural locations were identified.

At industrial and urban locations in Ontario in 1990, based on seven samples taken in five cities, concentrations of NDMA were all below the detection limit (detection limits ranged from 0.0034 to 0.0046 µg/m³).¹

In surveys during 1990 of ambient air in the vicinity of a chemical production facility in Elmira, Ontario, concentrations of NDMA in 41 samples ranged from not detected (detection limits ranged from 0.0029 to 0.0048 µg/m³) to 0.230 µg/m³; concentrations in 20 of the 41 samples were at or above the detection limit.¹ The highest concentrations were measured within the perimeter of the production facility, while the maximum concentration measured beyond this perimeter was 0.079 µg/m³. Concentrations of NDMA in samples taken

¹ Technical memorandum from A. Ng to G. De Brou dated 27 April 1990 regarding the Elmira (1990) survey: Results of the mobile TAGA; with covering memorandum dated 5 May 1990 from L. Lusia to E. Piché regarding the Elmira NDMA survey report, April 1990. Toronto, Ontario, Ontario Ministry of the Environment.

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in the vicinity of an industrial site in Kitchener, Ontario, were similar.¹

6.1.2 Indoor air

Available data indicate that levels of NDMA were elevated in indoor air contaminated with environmental tobacco smoke (ETS) in the USA (Brunnemann & Hoffmann, 1978) and Austria (Stehlik et al., 1982; Klus et al., 1992). The maximum concentration of NDMA in ETS-contaminated indoor air was $0.24 \mu\text{g}/\text{m}^3$, whereas NDMA was not detected (i.e., $<0.003 \mu\text{g}/\text{m}^3$) when the indoor air of a residence of a non-smoker was sampled in the same manner (Brunnemann & Hoffmann, 1978). Concentrations of NDMA in ETS-contaminated indoor air in these countries were generally between 0.01 and $0.1 \mu\text{g}/\text{m}^3$ (Health Canada, 1999).

6.1.3 Water

Releases of NDMA to water in Canada have been measured primarily in Ontario and vary considerably. As an example, in 1996, a chemical plant released wastewater containing NDMA into the St. Clair River at a concentration of $0.266 \mu\text{g}/\text{litre}$ (Environment Canada, 1997). In April 1997, concentrations of NDMA at the point of release to surface water ranged from 0.096 to $0.224 \mu\text{g}/\text{litre}$ for this company. These concentrations are expected to decrease, as the company installed a wastewater treatment plant in 1998.

In a survey of sewage treatment plant effluent in Ontario in 1990, NDMA was detected in 27 of 39 samples, with the maximum concentration being $0.22 \mu\text{g}/\text{litre}$ (OME, 1991).

In 390 samples of raw surface water from 101 water treatment plants sampled for NDMA in Ontario from 1990 to July 1998, concentrations were detectable ($>0.001 \mu\text{g}/\text{litre}$) in the raw water at 37 plants. The average concentration in raw water was $1.27 \times 10^{-3} \mu\text{g}/\text{litre}$. The highest concentration of NDMA in raw water was $0.008 \mu\text{g}/\text{litre}$ from two water treatment plants in 1996 (Ontario Ministry of Environment and Energy, unpublished data, 1996; P. Lachmaniuk, Ontario Ministry of the Environment, unpublished data, 1998).

In 1990, concentrations of NDMA in 24 ground-water samples taken from various locations in Ontario were below detection limits (detection limits ranged from 0.001 to $0.010 \mu\text{g}/\text{litre}$). Concentrations of NDMA in the municipal aquifer in Elmira ranged from 1.3 to $2.9 \mu\text{g}/\text{litre}$, attributed to contamination from a nearby chemical facility (Kornelsen et al., 1989). The municipal wells using this aquifer were closed in 1989 (Ireland, 1989). In 1994 and 1995, concentrations of up to $0.005 \mu\text{g}$ NDMA/litre (detection limit $0.001 \mu\text{g}/\text{litre}$) in raw surface water and groundwater supplies in rural areas in southern Ontario were reported (OME, 1991).

In 313 samples of treated water analysed from 100 locations within Ontario between 1994 and 1996, NDMA was detected (i.e., at greater than $0.001 \mu\text{g}/\text{litre}$) in at least one sample at 40 of these 100 sites. The censored mean concentration was $0.0027 \mu\text{g}/\text{litre}$. The highest concentrations were measured in samples from drinking-water plants using a specific pre-blended polyamine/alum water treatment coagulant (Ontario Ministry of Environment and Energy, unpublished data, 1996). These included a concentration of $0.04 \mu\text{g}/\text{litre}$ at the water treatment plant in Huntsville, Ontario. NDMA was detected in all (i.e., at greater than $0.001 \mu\text{g}/\text{litre}$) 20 samples collected from four water treatment plants using the specific coagulant. The mean concentration of NDMA in these 20 samples was $0.012 \mu\text{g}/\text{litre}$, whereas the (censored) mean concentration in the remaining 293 samples for the locations where the specific coagulant was not used was $0.002 \mu\text{g}/\text{litre}$.

Treatment studies on groundwater at a chemical plant in southern Ontario indicated that activated sludge can accumulate NDMA, particularly when nitrification and denitrification are applied to increase the age of the sludge. Concentrations of NDMA sampled in activated sludge ranged from 5 to $10 \text{ mg}/\text{litre}$ (J. Kochany, personal communication, 1999; E. McBean, personal communication, 1999). In the USA, NDMA has been reported to be a common constituent of sewage sludge. Concentrations ranged from 0.6 to $45 \mu\text{g}/\text{g}$ in the dried sludge from 14 of 15 cities (Mumma et al., 1984).

6.1.4 Sediment and soil

No data on concentrations of NDMA in sediments or soils in Canada were identified. Levels of NDMA up to $15.1 \text{ ng}/\text{g}$ have been measured in soils collected in the vicinity of industrial facilities in the USA (IARC, 1978).

6.1.5 Human tissues

NDMA has been quantified in a variety of tissues and biological fluids. In a study conducted in Quebec,

¹ Technical memorandum from A. Ng to M. Lusi dated 24 July 1992, regarding the Kitchener (1992) survey: NC Rubber Products Inc. — Results of the mobile TAGA 6000; with covering memorandum dated 28 July 1992, from M. Lusi to D. Ireland regarding the mobile TAGA 6000 survey of NC Rubber Products Inc. Toronto, Ontario, Ontario Ministry of the Environment.

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Canada, Cooper et al. (1987) detected NDMA in the liver, kidneys, brain, and pancreas from four (non-occupationally exposed) individuals at postmortem; concentrations ranged from approximately 0.12 to 0.9 ng/g tissue. In studies conducted outside of Canada, reported levels of NDMA in the blood or plasma of non-occupationally exposed individuals have ranged from approximately 0.03 to 1.5 ng/ml (Fine et al., 1977; Lakritz et al., 1980; Yamamoto et al., 1980; Garland et al., 1982; Gough et al., 1983; Dunn et al., 1986). In other studies, concentrations of NDMA in breast milk ranged from 0.1 to 1.8 ng/g (Lakritz & Pensabene, 1984; Mizuishi et al., 1987; Uibu et al., 1996). NDMA has been detected in the urine of individuals having no clearly defined exposure to this nitrosamine; reported concentrations from studies conducted in Canada (Kakizoe et al., 1979) and elsewhere (Lakritz et al., 1982; Webb et al., 1983) have ranged from 0.02 to 0.2 ng/ml.

6.1.6 Food

NDMA can be formed during food processing, preservation, and/or preparation from precursor compounds already present in, or added to, the specific food items. The foodstuffs that have been most commonly contaminated with NDMA can be classified into several broad groups:

- # foods preserved by the addition of nitrate and/or nitrite, such as cured meat products (in particular, bacon) and cheeses (since these methods of preservation introduce nitrosating species into the food);
- # foods preserved by smoking, such as fish and meat products (since oxides of nitrogen in the smoke act as nitrosating agents);
- # foods dried by combustion gases, such as malt, low-fat dried milk products, and spices (since combustion gases can contain oxides of nitrogen);
- # pickled and salt-preserved foods, particularly pickled vegetables (since microbial reduction of nitrate to nitrite occurs); and
- # foods grown or stored under humid conditions, leading to nitrosamine formation by contaminating bacteria.

It should be noted, however, that most data on levels of NDMA in foodstuffs have been derived from studies conducted in the 1970s and 1980s and may not be reliable with respect to estimating current exposure to this substance, owing to the analytical methodology available at the time. Moreover, efforts have been made to reduce the potential for exposure to NDMA in foodstuffs in Canada and other countries through continued reduction of allowable nitrite levels during preservation,

suspension of the use of nitrate for certain food groups, or increased use of nitrosation inhibitors, such as ascorbate or erythorbate (Cassens, 1997; Sen & Baddoo, 1997). For example, in Canada, in regulations amended in 1975, permissible levels of nitrite in cured meat products were lowered and the use of nitrate was eliminated, except for a few classes of products (including “slow-cured” meats) (G. Lawrence, personal communication, 1999). The use of nitrate in seafood preservation was suspended in 1965.¹

Data concerning the concentrations of NDMA in food items in Canada from each of the groups in which there is potential for exposure are limited and largely predate the introduction of controls outlined above. Concentrations of NDMA in 121 samples of various meat products in Canada ranged from less than 0.1 µg/kg (the limit of detection) to a maximum of 17.2 µg/kg in a sample of bacon (Sen et al., 1979, 1980b). Concentrations of NDMA in 63 samples of various fish and seafood products in Canada ranged from less than 0.1 µg/kg (the limit of detection) to a maximum of 4.2 µg/kg in a sample of salted/dried fish (Sen et al., 1985). Concentrations of NDMA in 62 samples of cheese (31 of Canadian origin and 31 imported) purchased in Canada ranged from less than 1 µg/kg (the limit of detection) to a maximum of 68 µg/kg in a sample of wine cheese (Sen et al., 1978).

NDMA was generally not detected in samples of milk products, except for skim milk powder, where it was present in all 11 samples, at a maximum concentration of 0.7 µg/kg (Sen & Seaman, 1981b). In other countries, the presence of NDMA in non-fat dried milk powders has been attributed to the use of natural gas for direct fired heating (Kelly et al., 1989; Scanlan et al., 1994). In Canada, in other foods dried directly, NDMA was detected in 1 of 10 samples of instant coffee at a concentration of 0.3 µg/kg and in 2 of 20 samples of dried soup with a maximum concentration of 0.25 µg/kg (Sen & Seaman, 1981b).

NDMA was not detected (at limits of detection ranging from 0.1 to 0.5 µg/kg) in 25 samples of baby food, including formula, cereal, and mixed food containing meat, analysed from 1979 to 1981 (Sen et al., 1979, 1980b; Sen & Seaman, 1981b). In a survey of other food products in 1979, NDMA was not detected in apple juice or drink, ketchup and other sauces, Ovaltine, margarine,

¹ Internal memorandum dated 13 September 1999 from J. Salminen, Bureau of Chemical Safety, Food Directorate, to B. Meek, Bureau of Chemical Hazards, Environmental Health Directorate, Health Canada, Ottawa, Ontario (File No. FP99072001-597).

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butter, lard, or (fresh and canned) mushrooms (Sen et al., 1980b). The limit of detection was 0.1 µg/litre or 0.1 µg/kg. NDMA was detected at a trace level (<0.2 µg/kg) in 1 of 11 samples of pizza and pizza toppings (Sen et al., 1980b).

Among the cured meat products analysed, bacon was unique, in that it was generally free of nitrosamines in the raw stage. Nitrosamines were formed in bacon only during high-heat frying (Sen et al., 1979). Various factors control the formation of NDMA in fried bacon, including the initial and residual levels of nitrite, processing conditions, the diet of the pigs, the lean to adipose tissue ratio, the presence of inhibitors, frying temperatures, and cooking methods (Sen, 1986). The cooked-out fat contains higher (approximately twice as high) levels of nitrosamines than the cooked lean bacon, and steam-volatile nitrosamines such as NDMA are volatilized in the fumes produced during frying (Sen, 1986).

Concentrations of NDMA in bacon currently consumed in Canada are unlikely to be as high as the maximum of 17.2 µg/kg reported previously (Sen et al., 1979, 1980b), as a result of the introduction of controls on the use of nitrate and nitrite in cured meat products in 1975. However, quantitative data are not available to support this conclusion.

There is consensus among the literature surveyed that concentrations of NDMA in foods from developed countries were an order of magnitude lower in the late 1980s and 1990s than in the 1970s (Tricker et al., 1991a; Cornée et al., 1992; Sen et al., 1996). The reduction in the concentrations of preformed NDMA in foods is attributed to improvements in food cooking and preservation techniques. However, no data are available with which to determine whether the concentrations of preformed NDMA in foods in Canada or elsewhere have continued to decline throughout the 1990s or remain at the levels measured in the late 1980s and 1990s.

Most malt beverages, including beer and most brands of whiskey, regardless of origin, contain NDMA (ATSDR, 1989). The presence of NDMA in beer was first reported in 1977 (Sen et al., 1980a; OME, 1991). Malt was found to be the main source of NDMA contamination in beer, and NDMA was shown to be formed during direct drying of malt using hot flue gases — a practice that was common prior to 1980 (Spiegelhalder et al., 1980). Improved malt drying techniques (direct to indirect in 1981) have now significantly reduced the levels of NDMA in malt and beer (OME, 1991; Sen et al., 1996). It is currently believed that NDMA is only a minor component of the total *N*-nitroso compounds in beer and

that the major contribution is made by as yet unidentified non-volatile *N*-nitroso compounds (Massey et al., 1990; UK MAFF, 1992). Among samples of beer produced in Canada, a maximum concentration of 4.9 µg/litre was reported in a beer from Ontario in 1978, while in more recent samples (i.e., 1988–1989), the maximum concentration was 0.59 µg/litre. Among imported beers purchased in Canada, a maximum concentration of 9.2 µg/litre was reported in a beer sampled in 1991–1992, while in more recent samples (i.e., October–December 1994), the maximum concentration was 3.2 µg/litre.

NDMA may also be endogenously produced *in vivo* from precursor compounds contained in the food ingested (e.g., DMA in meats and fish and nitrate/nitrite in vegetables) and/or already present in the human body (e.g., nitrate, nitrite) (Vermeer et al., 1998). However, available data are inadequate to serve as a basis for determining the quantities of endogenous NDMA formed or their relative contribution to exposure via ingestion compared with that from the exogenous presence of NDMA in food (Cornée et al., 1992).

6.1.7 Consumer products

Exposure can result from the use of consumer products that contain NDMA, such as cosmetics and personal care products, products containing rubber, and tobacco products.

NDMA has been detected in a variety of personal care and cosmetic products (e.g., shampoos, hair conditioners and toners, bath and shower gels, creams and oils, face tonics, cleansers), likely due to the reaction of nitrosating agents such as nitrite and/or nitrogen oxides, which occur frequently therein (Spiegelhalder & Preussmann, 1984), with amine-containing compounds, which are used extensively in ingredients of personal care products. Examples include surfactants, detergents, foam boosters, protein additives, and colouring agents (ECETOC, 1990). Nitrosation of precursor compounds in cosmetic matrices, which likely include quaternary ammonium compounds, betaines, and amine oxides (ECETOC, 1991), is often slow, but cosmetic products may remain on store shelves and in consumers' cabinets for extended periods of time, during which nitrosamines can continue to form in the products (Havery & Chou, 1994).

Fifty (or 34.5%) of 145 products surveyed in Germany in 1984 contained NDMA, at a maximum concentration of 24 µg/kg in one shampoo (Spiegelhalder & Preussmann, 1984). In some countries, controls have been introduced to limit levels of nitrosamines in cosmetics. For example, in Canada, manufacturers who

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submit cosmetic notifications for formulations that include combinations of such precursor substances are requested to provide evidence that the level of nitrosamines present in the product or formed over a period equivalent to the shelf life of the product does not exceed 10 µg/kg. Failing this, manufacturers are required to reformulate the products to remove either the amines/amides or the nitrosating agents (R. Green, personal communication, 1995).

Rubber-containing products that come into contact with human skin are another potential source of exposure to NDMA, since dialkylamines used in rubber vulcanization as accelerators and stabilizers can react with nitrosating agents to form nitrosamines (Biaudet et al., 1997). NDMA has been detected in a diverse selection of workplace, consumer, and medical products containing rubber (Health Canada, 1999). The maximum concentration of NDMA detected (i.e., 329 mg/kg) was in latex disposable protective gloves in the USA. However, only a small proportion of the total nitrosamines in the gloves would be expected to be leached out and dermally absorbed (Fiddler et al., 1985). *N*-Nitrosamines have been detected in baby bottle rubber nipples and pacifiers in Canada. The maximum concentrations of NDMA reported in the published literature were 25 mg/kg in baby bottle rubber nipples and 8.6 mg/kg in rubber pacifiers (Sen et al., 1984).

The nitrosation of natural constituents of tobacco during curing and fermentation results in the formation of three major classes of *N*-nitroso compounds in tobacco and tobacco products — volatile, non-volatile, and tobacco-specific *N*-nitrosamines (Hoffmann et al., 1984; Tricker et al., 1991b). In addition, the combustion of cigarette tobacco results in the pyrolytic formation of volatile *N*-nitrosamines, including NDMA (Tricker & Preussmann, 1992). The yields of these volatile *N*-nitrosamines in cigarette smoke from combustion of tobacco depend on many chemical and physical parameters, including the amounts of organic nitrogen and nitrate present (Hoffmann et al., 1987). Furthermore, nicotine serves as a specific precursor for formation of NDMA (Hoffmann et al., 1987).

The NDMA content of cigarette and oral tobacco and the amounts of NDMA in mainstream smoke, sidestream smoke, and ETS have been assessed in several studies (Health Canada, 1999). The levels of preformed volatile *N*-nitrosamines in the cigarette tobacco are considerably lower than the corresponding levels in the mainstream smoke (Tricker et al., 1991b), and the levels of NDMA in sidestream smoke are generally 1 or 2 orders of magnitude greater than in the mainstream smoke from the same cigarette (Health Canada, 1999).

The average ETS emission factor for NDMA for six US commercial cigarette brands was 570 ± 120 ng/cigarette (Daisey et al., 1994; Mahanama & Daisey, 1996). These data have been extrapolated to estimate the concentration of NDMA in indoor air spaces of defined volume and air exchange rates. The predicted concentrations of NDMA in indoor air ranged from 0.002 to 0.005 mg/m³ (Mahanama & Daisey, 1996). Predicted concentrations based on data from other studies ranged from 0.011 to 0.037 mg/m³ (Mahanama & Daisey, 1996). These modelled concentrations are similar to the measured concentrations of NDMA in indoor air contaminated with ETS, summarized in section 6.1.2.

6.2 Human exposure: environmental

Point estimates of daily intake (per kilogram body weight), based on available data that are limited in both spatial and temporal scope and reference values for body weight, inhalation volumes, and amounts of food and drinking-water consumed daily, are presented for six age groups in Table 2. These are ranges of reasonable worst-case estimates of daily intake, based on historic data, and indicate that daily intake of NDMA may be as high as 0.03 µg/kg body weight per day. It is not possible to develop defensible estimates of the current average daily intakes of NDMA for the general population due to the limitations of the (particularly recent) available Canadian data. If, despite these limitations, the lower ends of the ranges of reasonable worst-case estimates are considered upper bounds of average population exposure estimates, the daily intake of NDMA from outdoor air (in the vicinity of point sources), water, and food for the general population is unlikely to exceed 0.008 µg/kg body weight per day. Based on the assumptions underlying the reasonable worst-case estimates, most of the daily intake can be attributed to consumption of food contaminated with NDMA during processing, preservation, and/or preparation. It should be noted, though, that the data on which the estimates in food are based may not be representative of the situation today, due to the impact of subsequent introduction of changes in food processing and controls to limit formation in food. Intake of NDMA due to inhalation of air contaminated by atmospheric discharges from industrial point sources contributes somewhat less to the total daily intake,¹ and an even smaller contribution is attributed to consumption of drinking-water containing NDMA, based on a survey of

¹ Since NDMA was not detected in the one available survey of air not impacted by industrial point sources (i.e., Windsor, Ontario) (Ng & Karellas, 1994b), data were considered inadequate as a basis for estimation of the intake of NDMA in ambient air by the general population residing in an urban area, without point sources.

Table 2: Reasonable worst-case estimates of daily intake of NDMA by the general population in the sample country.

Media	Reasonable worst-case estimates of daily intake of NDMA ($\mu\text{g/kg}$ body weight per day)					
	0–0.5 years ^a	0.5–4 years ^b	5–11 years ^c	12–19 years ^d	20–59 years ^e	60+ years ^f
Air ^g	0.0005–0.005	0.001–0.011	0.0008–0.009	0.0004–0.005	0.0004–0.004	0.0003–0.004
Water ^h	0.0013–0.004	0.0006–0.002	0.0004–0.001	0.0002–0.001	0.0003–0.001	0.0003–0.001
Food ^{i,j}	0.0004–0.001 ^k	0.0065–0.016	0.0045–0.011	0.0036–0.009	0.0043–0.011	0.0036–0.009
Subtotals	0.0022–0.010 ^l	0.0081–0.029	0.0057–0.021	0.0042–0.015	0.005–0.016	0.0042–0.014
Indoor air–ETS ^m	0.06	0.13	0.10	0.06	0.05	0.04
Groundwater ⁿ	0.14–0.31	0.06–0.13	0.05–0.10	0.03–0.06	0.03–0.06	0.03–0.06
Beer ^o				<0.0002	0.0009	<0.0004
Shampoo ^p				0.00002	0.00002	0.00002

^a Assumed to weigh 7.5 kg, to drink 0.8 litres/day of total tap water (as infant formula), and to breathe 2.1 m³ of air per day (EHD, 1998).

^b Assumed to weigh 15.5 kg, to drink 0.7 litres/day of total tap water, and to breathe 9.3 m³ of air per day (EHD, 1998).

^c Assumed to weigh 31.0 kg, to drink 1.1 litres/day of total tap water, and to breathe 14.5 m³ of air per day (EHD, 1998).

^d Assumed to weigh 59.4 kg, to drink 1.2 litres/day of total tap water, and to breathe 15.8 m³ of air per day (EHD, 1998).

^e Assumed to weigh 70.9 kg, to drink 1.5 litres/day of total tap water, and to breathe 16.2 m³ of air per day (EHD, 1998).

^f Assumed to weigh 72.0 kg, to drink 1.6 litres/day of total tap water, and to breathe 14.3 m³ of air per day (EHD, 1998).

^g These reasonable worst-case estimates of intake by inhalation are based on short-term measurements of NDMA in outdoor air in the close vicinity of point sources of atmospheric discharge in Ontario. The minimum estimates are based on the lowest limit of detection (i.e., 0.0017 $\mu\text{g}/\text{m}^3$) for half-hour averaging times for Trace Atmospheric Gas Analyser (TAGA) measurements of NDMA in Kitchener, Ontario, in 1992 (technical memorandum from A. Ng to M. Lusi dated 24 July 1992 regarding the Kitchener (1992) survey: NC Rubber Products Inc. — Results of the mobile TAGA 6000; with covering memorandum dated 28 July 1992 from M. Lusi to D. Ireland regarding the mobile TAGA 6000 survey of NC Rubber Products Inc.; Toronto, Ontario, Ontario Ministry of the Environment). The maximum estimates are based on the censored mean concentration (i.e., 0.019 $\mu\text{g}/\text{m}^3$) for half-hour averaging times for TAGA measurements of NDMA ($n = 74$) in Elmira and Kitchener, Ontario (technical memorandum from A. Ng to M. Lusi dated 24 July 1992 [see above]; technical memorandum from A. Ng to G. De Brou dated 27 April 1990 regarding the Elmira (1990) survey: Results of the mobile TAGA; with covering memorandum dated 5 May 1990 from L. Lusi to E. Piché regarding the Elmira NDMA survey report, April 1990; Toronto, Ontario, Ontario Ministry of the Environment). Concentrations equivalent to one-half the appropriate limits of detection were assumed for half-hour averages during which NDMA was not detected. It was assumed that the population would be exposed to similar concentrations for 24 h daily, and that concentrations in the indoor air would be the same as those in outdoor air, in the immediate vicinity of the point sources.

^h These reasonable worst-case estimates of intake by ingestion of drinking-water are based on concentrations of NDMA measured in drinking-water in Ontario. The minimum estimates are based on the mean concentration (i.e., 0.012 $\mu\text{g}/\text{litre}$) for 20 samples from four water treatment plants in Ontario where elevated concentrations of NDMA were attributed to the use of a pre-blended polyamine/alum product in the water treatment plant (Ontario Ministry of Environment and Energy, unpublished data, 1996). The maximum estimates are based on the maximum concentration (i.e., 0.04 $\mu\text{g}/\text{litre}$) among these 20 samples, measured at the water treatment plant in Huntsville, Ontario (Ontario Ministry of Environment and Energy, unpublished data, 1996).

ⁱ Daily consumption rates (i.e., grams/person per day) of 181 food items by six age groups of Canadians (EHD, 1998) are the basis for the calculation of the reasonable worst-case daily intake of NDMA from ingestion of foods. In Canada, NDMA has been detected in 10 food items for which these daily consumption rates are available. (Intakes from an 11th food item [i.e., beer] are not included in these intake estimates.) The maximum concentrations of NDMA reported for each of the 10 food items (Sen et al., 1978, 1979, 1980b, 1985) were selected for calculation of the maximum estimates of intake from foods for the six age groups. Concentrations of NDMA in the remaining 171 food items were assumed to be zero.

^j The maximum concentrations in each of the 10 food items (i.e., referred to in footnote i) were reduced in proportion to the frequencies of detection of NDMA in the food item for calculation of the minimum estimates of intake from foods for the six age groups (EHD, 1998). The number of samples of each of the 10 food items referred to in footnote i ranged from 2 (for cottage cheese) to 55 (for cured pork). The frequencies of detection of NDMA in the 10 food items were calculated and ranged from 25% to 100%. Concentrations of NDMA in the remaining 171 food items were assumed to be zero.

^k The estimates of intake of NDMA by infants were based on the assumption that these infants consume table-ready foods at rates indicated in EHD (1998).

^l The total daily intake of NDMA by infants is overestimated, since the infants are assumed to be consuming both formula (i.e., reconstituted with drinking-water) and table-ready foods on a daily basis.

^m Based on the assumption that the population spends 21 h/day (EHD, 1998) breathing ETS-contaminated indoor air containing NDMA at the maximum reported concentration (0.24 $\mu\text{g}/\text{m}^3$) measured in a bar in the USA (Brunnemann & Hoffmann, 1978).

ⁿ Based on the minimum (1.3 $\mu\text{g}/\text{litre}$) and maximum (2.9 $\mu\text{g}/\text{litre}$) concentration of NDMA in well water in Elmira, Ontario (Kornelsen et al., 1989), resulting from contamination of groundwater by a nearby industrial facility, and average daily rates of water consumption (EHD, 1998).

^o Based on the most recent maximum concentration (0.59 $\mu\text{g}/\text{litre}$) of NDMA in Canadian beer (Sen et al., 1996) and average daily rates of intake of beer from EHD (1998). Intake from imported beer may be higher.

^p Dermal intake only. These estimates are based on the Canadian regulatory limit (i.e., 10 $\mu\text{g}/\text{kg}$) for nitrosamines in personal care products (R. Green, personal communication, 1995). Shampoo was selected, as the maximum reported concentration of NDMA (24 $\mu\text{g}/\text{kg}$) in such products has been in shampoo in Germany (Spiegelhalter & Preussmann, 1984). Dermal intake was estimated by a generalized approach involving product use scenarios (ECETOC, 1994).

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water treatment plants in Ontario. However, although possibly unrepresentative, available data indicate that contaminated groundwater in the vicinity of industrial point sources can, in some cases, lead to intakes that are greater than those from all other media combined.

If it is assumed that the population is exposed to the maximum concentration of NDMA in ETS-contaminated indoor air ($0.24 \mu\text{g}/\text{m}^3$) for 21 h/day (EHD, 1998), the upper-bounding estimates of intake by inhalation range from 0.04 to $0.13 \mu\text{g}/\text{kg}$ body weight per day. If it is assumed that an average adult smoker consumes 20 cigarettes a day and that the mainstream smoke contains between 4 and 278 ng/cigarette (Adams et al., 1987; Kataoka et al., 1997), the estimated intake of NDMA is $0.080\text{--}5.6 \mu\text{g}/\text{smoker}$ per day, or $0.001\text{--}0.08 \mu\text{g}/\text{kg}$ body weight per day. The upper end of this range of estimates of daily intake for smokers (i.e., $0.08 \mu\text{g}/\text{kg}$ body weight per day) is 5 times greater than the upper end of the range of reasonable worst-case estimates of intakes for adults from air, water, and food (i.e., $0.016 \mu\text{g}/\text{kg}$ body weight per day, as summarized in Table 2).

Reasonable worst-case estimates of daily intake of NDMA for all age groups from ingestion of contaminated groundwater range from 0.03 to $0.31 \mu\text{g}/\text{kg}$ body weight per day (see Table 2). These estimates are based on the minimum (i.e., $1.3 \mu\text{g}/\text{litre}$) and maximum (i.e., $2.9 \mu\text{g}/\text{litre}$) confirmed concentrations of NDMA in supply wells in Elmira, Ontario, in 1989 (Kornelsen et al., 1989). The groundwater was contaminated by discharges from a nearby industrial facility.

Estimates of daily intake of NDMA from ingestion of beer are not included in the reasonable worst-case estimates of intake from food in Table 2. For comparison, the most recent maximum concentration (i.e., $0.59 \mu\text{g}/\text{litre}$) of NDMA in Canadian beer¹ (Sen et al., 1996) and average daily rates of consumption of beer (EHD, 1998) are the basis for reasonable worst-case estimates of daily intake, which range from <0.0002 to $0.0009 \mu\text{g}/\text{kg}$ body weight per day.

Based on the limit (i.e., $10 \mu\text{g}/\text{kg}$) for nitrosamines in cosmetics in Canada (R. Green, personal communication, 1995), the potential dermal uptake of NDMA from a shampoo was estimated based on product use scenarios (ECETOC, 1994). A shampoo was selected for this calculation, as the maximum reported concentration (i.e., $24 \mu\text{g}/\text{kg}$) of NDMA in personal care products was in a shampoo in Germany (Spiegelhalder & Preussmann, 1984). The estimated uptake of $0.000\ 02 \mu\text{g}/\text{kg}$ body weight per day resulting from this calculation (Health Canada, 1999) is several orders of magnitude less than

the reasonable worst-case estimates of combined daily intakes from air, water, and food that are summarized in Table 2.

6.3 Human exposure: occupational

Although NDMA is not used directly, workplaces in which there is potential for exposure to NDMA (as a by-product of manufacturing processes) include, but are not necessarily limited to, leather tanneries, rubber and tire industries, rocket fuel industries, dye manufacturers, soap, detergent, and surfactant industries, foundries (core-making), fish processing industries (fish meal production), pesticide manufacturers, and warehouses and sales rooms (especially for rubber products) (ATSDR, 1989). Occupational exposure may result from inhalation or dermal contact (ATSDR, 1989). The National Occupational Exposure Survey (1981–1983) indicated that 747 workers, including 299 women, were potentially exposed to NDMA (NIOSH, 1984) in the USA. US Occupational Safety and Health Administration regulations concerning NDMA (OSHA, 1993) designate strict procedures to avoid worker contact. Mixtures containing $>1.0\%$ NDMA must be maintained in isolated or closed systems, workers must observe special hygiene rules, and certain procedures must be followed for movement of the material and in case of accidental spills or emergencies. Synthetic cutting fluids, semisynthetic cutting oils, and soluble cutting oils may contain nitrosamines, either as contaminants in amines or as products from reactions between amines and nitrite. Concentrations of nitrosamines ranging from 1 to $1000 \text{ mg}/\text{litre}$ have been determined in certain synthetic cutting oils. There are approximately 8–12 additives that could be responsible for nitrosamine formation in cutting oils. Approximately 750 000–780 000 workers employed by more than 1000 cutting fluid manufacturing firms are potentially exposed to nitrosamines in cutting oils. In addition, there is potential exposure of an undetermined number of machine shop workers who use these fluids. Kauppinen et al. (2000) estimated that in the early 1990s, about 14 000 workers in the European Union likely had occupational exposure to NDMA. Based upon monitoring studies conducted in a number of rubber manufacturing facilities in Europe, reported maximum concentrations of NDMA in workplace air have ranged from about $1 \mu\text{g}/\text{m}^3$ into the hundreds of micrograms per cubic metre (Ducos & Gaudin, 1986; Daubourg et al., 1992; Solionova et al., 1992; Rogaczewska & Wróblewska-Jakubowska, 1996; Oury et al., 1997; Straif et al., 2000).

¹ Intake from imported beer may be higher.

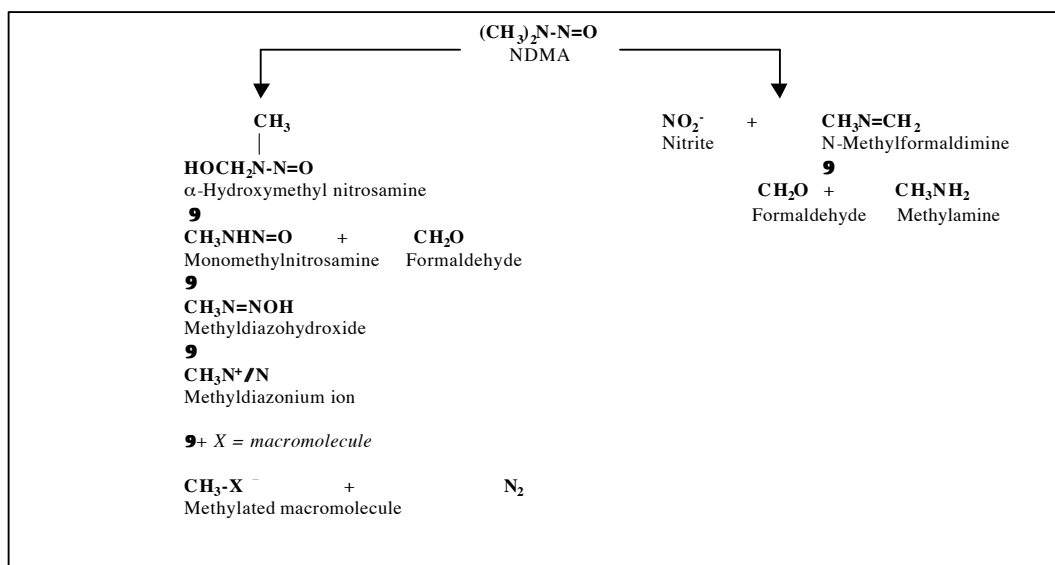


Figure 2: Pathways of NDMA metabolism
(adapted from ATSDR, 1989; Haggerty & Holsapple, 1990; Lee et al., 1996).

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

While quantitative data in humans have not been identified, on the basis of studies conducted with laboratory animals, ingested NDMA is absorbed rapidly and extensively (i.e., >90%) (Daugherty & Clapp, 1976; Diaz Gomez et al., 1977; Kunisaki et al., 1978), primarily from the lower intestinal tract (Phillips et al., 1975; Hashimoto et al., 1976; Agrelo et al., 1978; Pegg & Perry, 1981). Detection of NDMA in the urine of rats and dogs exposed by inhalation indicates that the nitrosamine is absorbed through the lungs; however, reliable quantitative information on the absorption of NDMA following inhalation was not identified. Although quantitative data were not identified, absorption through the skin may be inferred from the results of a study in which small amounts (i.e., 0.03%) of NDMA were detected in the urine of rats following epicutaneous (dermal) administration of a solution containing 350 μg NDMA (Spiegelhalder et al., 1982).

Once absorbed, NDMA and its metabolites are distributed widely (Daugherty & Clapp, 1976; Anderson et al., 1986) and likely passed to offspring through mothers' milk (Diaz Gomez et al., 1986). The nitrosamine and its metabolites have been detected in the fetuses of pregnant rodents injected with the substance (Althoff et al., 1977; Johansson-Brittebo & Tjälve, 1979). Pharmacokinetic analyses of NDMA injected intravenously into a number of laboratory species have

revealed that the nitrosamine is cleared rapidly from the blood, with metabolism involving both hepatic and extrahepatic components. NDMA and its metabolites may be excreted in the urine or exhaled as carbon dioxide.

Quantitative information from studies on the metabolism of NDMA in individuals was not identified. However, based upon a few studies in which the metabolic conversion of NDMA in human liver preparations has been examined, there appear to be no qualitative differences in the metabolism of NDMA between humans and laboratory animals. The metabolism of NDMA involves either the α -hydroxylation or denitrosation of the nitrosamine (Figure 2). Both pathways are considered to proceed through a common intermediate radical $[\text{CH}_3(\text{CH}_2\dot{\text{C}}\text{N}-\text{N}=\text{O})]$, generated by the action of the cytochrome P450 [CYP2E1]-dependent mixed-function oxidase system (Haggerty & Holsapple, 1990; Lee et al., 1996). Along the α -hydroxylation pathway, the hydroxymethylnitrosamine ($\text{HOCH}_2\text{CH}_2\text{N}-\text{N}=\text{O}$) formed from the intermediate radical decomposes to formaldehyde (itself ultimately converting to carbon dioxide) and monomethylnitrosamine ($\text{CH}_3\text{NHN}=\text{O}$); the monomethylnitrosamine, owing to its instability, undergoes rearrangement to the strongly methylating methyldiazonium ion ($\text{CH}_3\text{N}^+/\text{N}$), which alkylates biological macromolecules such as DNA, RNA, and proteins. Metabolic conversion of the intermediate radical via denitrosation may lead to the formation of methylamine (CH_3NH_2) and formaldehyde.

8. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

NDMA has been consistently potentially carcinogenic in all experimental species examined. Since exposure to NDMA occurs principally through its occurrence as a contaminant in media to which the general population is exposed, this end-point is expected to be limiting; hence, the focus of testing and, as a result, assessment has been carcinogenicity. Other end-points have not been well investigated; available data are considered inadequate as a basis for their meaningful characterization. In addition, exposure in available studies has been restricted primarily to ingestion; hence, meaningful dose-response analyses for other routes of exposure, even for the critical end-point (e.g., carcinogenicity), are precluded.

8.1 Single exposure

NDMA is highly acutely toxic after oral administration to rats, with LD₅₀s ranging from 23 to 40 mg/kg body weight. It is also highly acutely toxic via inhalation; 4-h LC₅₀s are 78 ppm (240 mg/m³) for rats and 57 ppm (176 mg/m³) for mice. One day after three dogs were exposed (via inhalation) to 16 ppm (49 mg/m³) NDMA for 4 h, one had died, and the others were moribund (ATSDR, 1989). In all three species, acute inhalation exposure produced haemorrhagic necrosis in the liver; an increased blood clotting time was reported for the NDMA-exposed dogs (ATSDR, 1989). Following intraperitoneal exposure, LD₅₀s of 43 mg/kg body weight in rats and 20 mg/kg body weight in mice have been reported (IARC, 1978). In other laboratory species, acute exposure to NDMA produced effects in the liver (hepatotoxicity), kidney (tumours), and testes (necrosis of the seminiferous epithelium) (Magee & Barnes, 1962; Schmidt & Murphy, 1966; Hard & Butler, 1970a,b; McLean & Magee, 1970; OME, 1991).

8.2 Irritation and sensitization

Data on the potential of NDMA to induce sensitization and/or irritation were not identified.

8.3 Short- and medium-term exposure

Hepatic effects (i.e., hepatocyte vacuolization, portal venopathy, and necrosis/haemorrhage), often associated with reduced survival, have been observed in a number of mammalian species exposed orally under various conditions (e.g., in rats receiving 1, 3.8, or 5 mg NDMA/kg body weight per day for 30, 7–28, or 5–11 days, respectively; in mice receiving 5 mg/kg body weight per day for 7–28 days; in hamsters receiving 4 mg/kg body weight per day for 1–28 days; in guinea-

pigs, cats, and monkeys receiving 1 mg/kg body weight per day for 30 days or 5 mg/kg body weight per day for 5–11 days; in dogs receiving 2.5 mg/kg body weight per day, 2 days/week, for 3 weeks; and in mink receiving 0.32 mg/kg body weight per day for 23–34 days) (summarized from IARC, 1978; ATSDR, 1989).

In addition to effects in the liver, “congestion” in a variety of organs (i.e., kidneys, lung, spleen, and myocardium) has been reported following examination of rats receiving 3.8 mg NDMA/kg body weight per day in the diet for 1–12 weeks (Khanna & Puri, 1966). Gastrointestinal haemorrhage has been observed in rats receiving dietary doses of 10 mg NDMA/kg body weight per day for 34–37 days (Barnes & Magee, 1954) and in mink receiving 0.3 or 0.6 mg NDMA/kg body weight per day in the diet for 23–34 days (Carter et al., 1969). Effects in the kidneys (including glomerulus dilatation and slight thickening of the Bowman’s capsule) were observed in mink receiving 0.2 mg NDMA/kg body weight per day from the diet (period not specified) (Martino et al., 1988).

8.4 Carcinogenicity

Although most studies would be considered limited by current standards (e.g., small group sizes, single dose levels, limited histopathological examination), there has been clear, consistent evidence of carcinogenicity in a number of studies in which rodents (i.e., rats, mice, hamsters) were exposed to NDMA orally, via inhalation, or by intratracheal instillation. NDMA increased the incidence of liver and Leydig cell tumours in rats ingesting this nitrosamine from drinking-water or the diet (Terao et al., 1978; Arai et al., 1979; Ito et al., 1982; Lijinsky & Reuber, 1984); increased tumour incidences were noted at concentrations of NDMA of about 5 mg/litre in drinking-water and 10 mg/kg in the diet. Increased incidences of nasal, hepatic, pulmonary, and renal tumours were observed in rats exposed to NDMA via inhalation (Moiseev & Benemanskii, 1975; Klein et al., 1991); increases in the incidence of hepatic, pulmonary, and renal tumours were observed following exposure to NDMA at a concentration of 0.2 mg/m³ (Moiseev & Benemanskii, 1975). Hepatic, pulmonary, and renal carcinogenicity was observed in mice administered NDMA via drinking-water (Terracini et al., 1966; Clapp & Toya, 1970; Anderson et al., 1979, 1986, 1992) or through inhalation (Moiseev & Benemanskii, 1975); increases in tumour incidence were observed at concentrations of NDMA in drinking-water ranging from 0.01 to 5 mg/litre. Moreover, in some cases (e.g., Terracini et al., 1966), the period of exposure to NDMA was relatively short (i.e., 3 weeks). NDMA increased the incidence of liver tumours in hamsters exposed intratracheally (Tanaka et al., 1988). The administration of NDMA to pregnant rats (by intraperitoneal injection) or mice (by stomach tube) increased the frequency of

hepatic and renal tumours in the offspring (Alexandrov, 1968; Anderson et al., 1989). An increased incidence of renal tumours has also been observed in rats administered either a single oral (Magee & Barnes, 1962) or intraperitoneal (Hard & Butler, 1970a; McLean & Magee, 1970) dose of NDMA (at levels of 30–60 mg/kg body weight).

In a more recently conducted comprehensive carcinogenicity bioassay (designed to provide detailed information on exposure–response) involving lifetime exposure, 15 dose groups of 60 male and 60 female Colworth-Wistar rats were provided with drinking-water containing a wide range of concentrations of NDMA¹ (Tables 3 and 4) (Brantom, 1983; Peto et al., 1991a,b). The estimated daily intakes of NDMA ranged from 0.001 to 0.697 mg/kg body weight in the males and from 0.002 to 1.224 mg/kg body weight in the females. A control group of 120 males and 120 females received drinking-water without NDMA (Brantom, 1983; Peto et al., 1991a,b). Groups of animals were taken for interim sacrifice after 12 and 18 months of study. Survival of the animals was reduced with increasing dose; animals in the highest dose group did not survive longer than 1 year. There were no significant differences in body weight between the exposed animals and the controls. Dose-related increases in tumour incidence were observed only in the liver in both males and females (see Tables 3 and 4). The increase in tumour incidence was greatest for hepatocellular carcinoma and biliary cystadenoma. Non-neoplastic effects observed in the liver included hyperplastic nodules and the shrinkage of hepatocytes.

8.5 Genotoxicity and related end-points

In numerous studies conducted *in vitro* in bacterial and mammalian cells, there has been overwhelming evidence that NDMA is mutagenic and clastogenic (reviewed in IARC, 1978; ATSDR, 1989). Increased frequencies of gene mutations, chromosomal damage, sister chromatid exchange, and unscheduled DNA synthesis have been observed in a wide variety of cell types, in assays conducted in the presence or absence of metabolic activation. Positive results have been observed in human as well as rodent cells.

Similarly, clear evidence of genetic effects has also been observed in *in vivo* studies. Clastogenic effects (e.g., micronuclei, sister chromatid exchange, chromosomal aberrations) in hepatocytes (Tates et al., 1980, 1983, 1986; Mehta et al., 1987; Braithwaite & Ashby,

1988; Cllet et al., 1989; Neft & Conner, 1989; Sawada et al., 1991), bone marrow cells (Bauknecht et al., 1977; Wild, 1978; Neal & Probst, 1983; Collaborative Study Group for the Micronucleus Test, 1986; Neft & Conner, 1989; Krishna et al., 1990; Sato et al., 1992; Morrison & Ashby, 1994), spleen cells (Neft & Conner, 1989; Krishna et al., 1990), and peripheral blood lymphocytes (Tates et al., 1983; Sato et al., 1992), as well as in oesophageal (Mehta et al., 1987) and kidney cells (Robbiano et al., 1997), have been observed in rodents (rats, mice, or hamsters) administered NDMA either orally or by intraperitoneal injection. Increased frequencies of micronucleated cells were observed at doses as low as 5 mg/kg body weight in rats (Trzos et al., 1978; Mehta et al., 1987). Effects in germ cells (i.e., micronucleated spermatids) were observed in mice given 6 or 9 mg NDMA/kg body weight via intraperitoneal injection (Cllet et al., 1993). The inhalation exposure of female mice to 1030 mg NDMA/m³ increased the frequency of micronucleated bone marrow cells (Odagiri et al., 1986). Evidence of genotoxicity (e.g., chromosomal aberrations, micronuclei, gene mutation, DNA strand breaks) has also been observed in the offspring of hamsters (Inui et al., 1979) and mice (Bolognesi et al., 1988) administered NDMA during gestation.

In rodents (rats, mice, or hamsters) administered NDMA either orally or by intraperitoneal injection, evidence of DNA damage has been observed in the liver, kidneys, and lungs (Laishes et al., 1975; Petzold & Swenberg, 1978; Abanobi et al., 1979; Mirsalis & Butterworth, 1980; Brambilla et al., 1981, 1987; Bermudez et al., 1982; Cesarone et al., 1982; Barbin et al., 1983; Doolittle et al., 1984; Kornbrust & Dietz, 1985; Loury et al., 1987; Mirsalis et al., 1989; Pool et al., 1990; Brendler et al., 1992; Jorquera et al., 1993; Asakura et al., 1994; Tinwell et al., 1994; Webster et al., 1996). DNA damage in thymus (Petzold & Swenberg, 1978), sperm (Cesarone et al., 1979), and nasal and tracheal cells (Doolittle et al., 1984) has also been noted. NDMA was mutagenic at the *lacI* locus (in the liver) in *in vivo* assays involving transgenic mice (Mirsalis et al., 1993; Tinwell et al., 1994; Butterworth et al., 1998). Effects (i.e., increased unscheduled hepatic DNA synthesis) have been observed in rats at doses as low as 0.1 mg NDMA/kg body weight (Mirsalis & Butterworth, 1980).

¹ The concentrations of NDMA were 33, 66, 132, 264, 528, 1056, 1584, 2112, 2640, 3168, 4224, 5280, 6336, 8448, and 16 896 µg/litre.

Concise International Chemical Assessment Document 38**Table 3: Carcinogenicity study with male rats.^a**

Exposure group	NDMA concentration in drinking-water (mg/litre)	Estimated intake (mg/kg body weight per day) ^b	Animals with hepatic tumours (%) ^c		
			Carcinoma	Haemangiosarcoma	Biliary cystadenoma
1	0	0	1	1	1
2	0.033	0.001	2	0	4
3	0.066	0.003	2	0	4
4	0.132	0.005	4	2	4
5	0.264	0.011	2	4	4
6	0.528	0.022	6	0	2
7	1.056	0.044	10	2	2
8	1.584	0.065	13	2	8
9	2.112	0.087	10	13	13
10	2.640	0.109	25	13	23
11	3.168	0.131	29	29	27
12	4.224	0.174	33	21	25
13	5.280	0.218	58	6	29
14	6.336	0.261	60	15	40
15	8.448	0.348	77	6	29
16	16.896	0.697	88	6	4

^a Brantom (1983); Peto et al. (1991a,b). Animals were provided, for their entire lives until natural death, drinking-water containing the indicated concentrations of NDMA. The animals were sacrificed and necropsied if moribund or exhibiting palpable liver alterations.

^b Intakes estimated by authors (Peto et al., 1991b).

^c Proportion of animals with tumours specified at each dose level; $n = 192$ for unexposed controls (treatment group 1); $n = 48$ for each dose level (treatment groups 2–16) (Brantom, 1983).

8.6 Reproductive toxicity

Available data are inadequate as a basis for assessment of the reproductive or developmental toxicity of NDMA. Interpretation of the results of most identified investigations is complicated by the high doses administered, likely to have induced acute or repeated-dose organ toxicity. In a report by Anderson et al. (1978), time to conception in female mice provided with drinking-water containing 0.1 mg NDMA/litre for 75 days prior to mating was about 3 days longer than in unexposed controls; no other reproductive effects were assessed in this study. In a study conducted with male rats, a single intraperitoneal injection of 30 or 60 mg NDMA/kg body weight induced testicular damage (necrosis or degeneration of the seminiferous epithelium) (Hard & Butler, 1970b).

In a single-generation study (Anderson et al., 1978) in which the reproductive effects of a number of substances were examined, groups of 20 female mice were provided with drinking-water containing 0 or 0.1 mg NDMA/litre for 75 days prior to mating and throughout pregnancy and lactation (estimated daily and total

intakes of 0.02 mg/kg body weight per day and 2 mg/kg body weight, respectively). The proportion of deaths (based upon the total number of stillborn and neonatal deaths) was increased ($P < 0.05$) 2-fold in the NDMA-exposed animals compared with controls (i.e., 20% and 9.9%, respectively), due in large part to an increase in the number of stillborn animals. Exposure to NDMA had no effect upon maternal fluid consumption, litter size, or average body weight of the weanlings, and no consistent gross or histopathological abnormalities were observed in the stillborn fetuses or dead neonates to account for the increased mortality. In a somewhat more recent study with mice administered higher doses of the nitrosamine, a single intraperitoneal injection of 37 mg NDMA/kg body weight on day 16 or 19 of gestation resulted in the deaths of all fetuses in exposed dams; information on maternal toxicity was not provided (Anderson et al., 1989). Notably, this dose is greater than the LD_{50} for this route in these animals of 20 mg/kg body weight (IARC, 1978). In the same study, lethality was not observed following the administration of 7.4 mg NDMA/kg body weight (Anderson et al., 1989).

Table 4: Carcinogenicity study with female rats.^a

Exposure group	NDMA concentration in drinking-water (mg/litre)	Estimated intake (mg/kg body weight per day) ^b	Animals with hepatic tumours (%) ^c		
			Carcinoma	Haemangiosarcoma	Biliary cystadenoma
1	0	0	1	1	2
2	0.033	0.002	0	2	2
3	0.066	0.005	0	0	8
4	0.132	0.010	4	2	0
5	0.264	0.019	4	0	6
6	0.528	0.038	10	2	10
7	1.056	0.076	6	4	15
8	1.584	0.115	10	2	71
9	2.112	0.153	10	6	69
10	2.640	0.191	8	2	83
11	3.168	0.229	13	6	92
12	4.224	0.306	15	4	90
13	5.280	0.382	25	0	85
14	6.336	0.459	38	0	69
15	8.448	0.612	69	6	33
16	16.896	1.224	73	10	8

^a Brantom (1983); Peto et al. (1991a,b). Animals were provided, for their entire lives until natural death, drinking-water containing the indicated concentrations of NDMA. The animals were sacrificed and necropsied if moribund or exhibiting palpable liver alterations.

^b Intakes estimated by authors (Peto et al., 1991b).

^c Proportion of animals with tumours specified at each dose level; *n* = 192 for unexposed controls (treatment group 1); *n* = 48 for each dose level (treatment groups 2–16) (Brantom, 1983).

Fetal body weight was significantly ($P < 0.05$) reduced after a single oral dose of 20 mg NDMA/kg body weight was administered to pregnant rats on day 15 or 20 of gestation (Nishie, 1983). Although information on fetal survival or teratogenicity was not provided, toxic effects (reduced weight gain, hepatotoxicity, and death) were observed among the dams. Fetal deaths were noted in a number of studies (cited in ATSDR, 1989) conducted with rats in which NDMA was administered to pregnant dams 1) as a single oral dose (30 mg/kg body weight) on one of days 1–12 (Alexandrov, 1974) or 1–15 (Napalkov & Alexandrov, 1968) of gestation; 2) as repeated gavage doses of 1.4–2.9 mg/kg body weight per day for 7 or more days during gestation (Napalkov & Alexandrov, 1968); or 3) in the diet (intake of 5 mg/kg body weight per day) from an unspecified day of pregnancy to sacrifice on day 20 of gestation (Bhattacharyya, 1965). Although no teratogenic effects were reported in these studies, interpretation of these investigations is difficult owing to insufficient information on experimental design and results, lack of controls, and lack of information on maternal toxicity (ATSDR, 1989). The doses administered in some of these studies were close to the LD₅₀.

8.7 Neurotoxicity and effects on the immune system

Data concerning effects on the brain or central nervous system in animals exposed to NDMA were not identified.

Similarly, available data are inadequate as a basis for assessment of the immunological effects of NDMA. Interpretation of the results of most identified investigations is complicated by likely toxicity associated with the high doses administered. In studies in which B6C3F₁ female mice were administered repeated intraperitoneal injections of 1.5, 3, or 5 mg NDMA/kg body weight per day for 14 days, observed effects on the immune system included suppression of humoral immunity with declines in the IgM antibody-forming cell response to sheep red blood cells and reductions in splenocyte proliferation in response to lipopolysaccharide (reviewed in Haggerty & Holsapple, 1990). Also observed were reductions in T-lymphocyte function (i.e., reduced cell-mediated immunity) with a decline in proliferative responses to various T-cell mitogenic stimuli, suppression of the mixed lymphocyte response, and selected delayed hypersensitivity responses, as well as significant reductions in host resistance to infection with *Listeria monocytogenes*, *Streptococcus zooepidemicus*, or the influenza virus or

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to challenge with B16F10 tumour cells. Reductions in antibody formation and *in vitro* lymphoproliferative responses were observed in male BALB/c mice administered 5 mg NDMA/kg body weight intraperitoneally for 14 days (Jeong & Lee, 1998).

Female CD-1 mice provided with drinking-water containing 5 or 10 mg NDMA/litre for 30–120 days exhibited marked suppression of humoral- and cell-mediated immunity (Desjardins et al., 1992); however, effects were reversible within 30 days of cessation of exposure. No effects were observed in animals consuming drinking-water containing 1 mg NDMA/litre.

8.8 Mode of action

There is strong evidence that the toxicological effects of NDMA are directly dependent upon the CYP2E1-dependent metabolic conversion of this nitrosamine to highly reactive species. Lee et al. (1996) attributed the hepatotoxicity of NDMA to the methyl-diazonium ion formed via the α -hydroxylation pathway; denitrosation was considered to make little contribution to the overall hepatotoxic effect of this nitrosamine in rats. The principal DNA adduct formed following exposure to NDMA is *N*⁷-methylguanine (representing about 65% of all adducts formed initially upon exposure); *O*⁶-methylguanine is a secondary adduct (representing about 7% of all adducts formed initially). Other DNA adducts formed in smaller amounts include *N*³-methyladenine and *O*⁴-methylthymine.

*N*⁷-Methylguanine may undergo depurination yielding apurinic sites, which, if not repaired prior to DNA replication, can result in guanine to thymine transversions (Swenberg et al., 1991). *O*⁶-Methylguanine and *O*⁴-methylthymine (formed at about 1% of the amount of *O*⁶-methylguanine) are strongly promutagenic by direct mispairing. *O*⁶-Methylguanine gives rise to guanine: cytosine to adenine:thymine (i.e., G:C to A:T) transitions, while *O*⁴-methylthymine causes A:T to G:C transitions (Swenberg et al., 1991; Souliotis et al., 1995).

Available data are consistent with the formation and persistence of the secondary adduct, *O*⁶-methylguanine, being associated with both the carcinogenicity and mutagenicity of NDMA (reviewed in Haggerty & Holsapple, 1990; Swenberg et al., 1991; Souliotis et al., 1995). The ability of cells to repair DNA adducts (by removing *O*⁶-methylguanine through the action of a specific *O*⁶-methylguanine DNA-methyltransferase) prior to cell division likely plays a critical role in determining the susceptibility of tissues to tumour development.

In monkeys administered (orally) 0.1 mg NDMA/kg body weight, *O*⁶-methylguanine was detected in 32 tissues examined (Anderson et al., 1996). The highest

levels were in the gastric mucosa and liver, but elevated levels were also present in white blood cells, the oesophagus, ovaries, pancreas, bladder, and uterus. *O*⁶-Methylguanine DNA-methyltransferase activity varied over a 30-fold range; the highest activities were in the gastric mucosa, liver, kidneys, and lungs. The formation of *O*⁶-methylguanine was detected in fetal liver, lung, kidney, spleen, and brain in a study in which pregnant patas monkeys were administered (intragastrically) a single dose of 1 mg NDMA/kg body weight (Chhabra et al., 1995).

The greater persistence of *O*⁶-methylguanine DNA adducts in the kidney compared with the liver in rats administered a single oral dose of 20 mg NDMA/kg body weight parallels earlier findings in which the acute oral or intraperitoneal administration of NDMA to rats at such dose levels increased the incidence of kidney but not liver tumours (Magee & Barnes, 1962; Schmidt & Murphy, 1966; Hard & Butler, 1970a; McLean & Magee, 1970). In contrast, the long-term oral administration of low doses of NDMA (i.e., <2 mg/kg body weight per day) increased the incidence of liver but not kidney tumours in these animals (Brantom, 1983; Lijinsky & Reuber, 1984; Peto et al., 1991a,b), a finding attributed to the first-pass metabolism of NDMA in the liver (Swenberg et al., 1991).

There are quantitative age- and species-related differences in hepatic *O*⁶-methylguanine, possibly associated with variations in the activity of the transferase, consistent with observed variations in the carcinogenicity of the compound among species and strains exposed under various conditions. These include greater hepatic activity in adults versus newborn mice (Coccia et al., 1988), in rats versus mice (Lindamood et al., 1984), and between strains of mice (greater in C3H than in C57BL) (Lindamood et al., 1984).

Evidence supporting a role for *O*⁶-methylguanine formation in tumour development following exposure to NDMA was recently reviewed by Souliotis et al. (1995). G:C to A:T transitions have been observed in the *ras* oncogene in mouse lung tumours induced by NDMA (Devereux et al., 1991), in the livers of *lacI* transgenic mice administered a single dose of 4 mg NDMA/kg body weight (Mirsalis et al., 1993), and in the liver, kidney, and lung of *lacI* transgenic mice administered five daily doses of 1 mg NDMA/kg body weight (Wang et al., 1998). Moreover, transgenic mice expressing high levels of *O*⁶-methylguanine DNA-methyltransferase in the liver were less susceptible than normal controls to NDMA-induced hepatocarcinogenesis (Nakatsuru et al., 1993). However, Souliotis et al. (1995) also reported that the dose-response relationship for the accumulation of *O*⁶-methylguanine in hepatic DNA in rats administered drinking-water (for 28 days) containing concentrations

of NDMA similar to those used in the study conducted at BIBRA Toxicology International (Brantom, 1983; Peto et al., 1991a,b) did not strictly parallel the dose–response for the development of hepatic tumours in the carcinogenicity bioassay.

9. EFFECTS ON HUMANS

Two deaths linked to the acute ingestion of NDMA, as well as a third attributed to the consumption of at least four doses of approximately 250–300 mg NDMA over a 2-year period, have been reported (Fussgänger & Ditschuneit, 1980; Pedal et al., 1982). Liver failure was observed in all three cases; the two acutely exposed decedents also exhibited cerebral haemorrhage. In two fatalities involving exposure to unknown concentrations of NDMA fumes, a tender and enlarged liver, splenic enlargement, abdominal distension, and the accumulation of yellow fluid in the peritoneal cavity were observed in one man prior to death (Freund, 1937); in the other death, liver cirrhosis was observed at autopsy (Hamilton & Hardy, 1974). In two other non-fatal cases involving exposure to NDMA fumes, effects included jaundice, the accumulation of fluid in the peritoneal cavity, exhaustion, headaches, abdominal cramps, soreness on the left side, nausea, and vomiting (Freund, 1937; Hamilton & Hardy, 1974).

Relevant epidemiological studies include case–control investigations in which the potential risks of cancer of the stomach (Risch et al., 1985; González et al., 1994; La Vecchia et al., 1995; Pobel et al., 1995), upper digestive tract (Rogers et al., 1995), and lung (Goodman et al., 1992; De Stefani et al., 1996) associated with the ingestion of NDMA have been assessed. In some of these reports (Goodman et al., 1992; González et al., 1994; Pobel et al., 1995), the estimated intake of NDMA was based upon recollection of an individual's typical diet consumed in the year preceding the onset of illness, as well as the reported levels of this nitrosamine in the foodstuffs consumed, derived from other studies. In the studies conducted by De Stefani et al. (1996) and Rogers et al. (1995), subjects were asked to recall their typical diet in the 5 and 10 years, respectively, prior to the onset of illness.

In three of four case–control studies,¹ there was a positive relationship with evidence of exposure–response for the intake of NDMA and gastric cancer (González et al., 1994; La Vecchia et al., 1995; Pobel et al., 1995), although not in an additional study in which oral, laryngeal, and oesophageal cancers were investigated separately (Rogers et al., 1995). In two case–control studies² in which matching or control for confounders was rather more extensive than that for the investigations of gastric cancer mentioned above, there were clear exposure–response relationships for NDMA and lung cancer (Goodman et al., 1992; De Stefani et al., 1996). In almost all studies, associations between the cancers of interest and nitrate, nitrite, and NDMA were examined; results were relatively consistent in this regard, with there being an association with cancer most commonly with NDMA; results for nitrite were mixed, and there was an inverse association with nitrate.

In a population-based cohort study that assessed the risks of head and neck, stomach, and colorectal cancer associated with the dietary intake of NDMA, the relative risk (RR) of colorectal cancer was increased for

¹ In González et al. (1994), the odds ratios (ORs) for gastric cancer were 1, 1.86, 1.79, and 2.09 among individuals with intakes of NDMA in the first (reference group), second, third, and fourth quartiles, respectively ($P = 0.007$ for trend). Pobel et al. (1995) reported ORs (95% confidence intervals [CIs]) (adjusted for age, sex, occupation, and total caloric intake) of 1, 4.13 (0.93–18.27), and 7.0 (1.85–26.46) among individuals with intakes of NDMA in the first (reference group), second, and third tertiles, respectively ($P = 0.04$ for trend). In La Vecchia et al. (1995), ORs (95% CIs) (adjusted for age, sex, education, family history of gastric cancer, combined food score index, intake of β -carotene, vitamin C, nitrite, nitrate, and total calories) for stomach cancer were 1, 1.11 (0.9–1.4), and 1.37 (1.1–1.7) among individuals with intakes of NDMA in the first (reference group), second, and third tertiles, respectively ($P < 0.01$ for trend).

² In Goodman et al. (1992), ORs (95% CIs) (adjusted for age, ethnic group, smoking status, pack-years of cigarette use, and β -carotene intake) for those in the second, third, and fourth quartiles of NDMA intake (compared with the first quartile) were (among men) 1.7 (0.9–3.2), 2.8 (1.4–5.3), and 3.3 (1.7–6.2) and (among women) 1.4 (0.7–2.9), 1.8 (0.7–4.2), and 2.7 (1.0–6.9), respectively (trends were $P = 0.006$ and 0.04 for males and females, respectively). De Stefani et al. (1996) reported ORs (95% CIs) for all types of lung cancer (combined) among individuals in the first, second, third, and fourth quartiles of NDMA intake of 1, 0.88 (0.53–1.48), 1.77 (1.06–2.96), and 3.14 (1.86–5.29), respectively ($P < 0.001$ for trend).

the group having the highest intake of NDMA¹ (Knekt et al., 1999). The highest intake group had increased and reduced RRs of head and neck (RR = 1.37; 95% CI = 0.5–3.74) and stomach cancer (RR = 0.75; 95% CI = 0.37–1.51), respectively, compared with the lowest quartile (reference group).

There appears to be no qualitative difference between rodents and humans in the formation of DNA adducts following exposure to NDMA. In a case of suspected NDMA poisoning in a human male, methylation of liver DNA was evident at both the *N*⁷ and *O*⁶ positions of guanine (Herron & Shank, 1980). Using an immunohistochemical technique, Parsa et al. (1987) detected the formation of *O*⁶-methylguanine in human pancreatic explants incubated *in vitro* with NDMA.

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

10.1 Aquatic environment

Green algae (*Selenastrum capricornutum*) and blue-green algae (*Anabaena flos-aqua*) were exposed to NDMA over a 13-day period in static systems. The test was conducted to determine effects on algal growth rate, cell number, maximum standing crop, and dry weight. The 13-day EC₅₀s for growth were 4 mg/litre and 5.1 mg/litre for the green and blue-green algae, respectively (Draper & Brewer, 1979).

Draper & Brewer (1979) reported a 96-h LC₅₀ of 940 mg/litre for fathead minnow (*Pimephales promelas*) and a 96-h LC₅₀ of 1365 mg/litre for flatworms (*Dugesia dorotocephala*). For scud (*Gammarus limnaeus*), 96-h LC₅₀ values ranged from 280 to 445 mg/litre (Draper & Fisher, 1980). Both studies were conducted in static renewal systems.

The LC₅₀ values for a saltwater fish, the common mummichog (*Fundulus heteroclitus*), in a static non-renewal system were 8300 mg/litre at 24 h, 5500 mg/litre at 48 h, 4700 mg/litre at 72 h, 3300 mg/litre at 96 h, and 2700 mg/litre at 120 h (Ferraro et al., 1977).

Grieco et al. (1978) reported a dose-related increase in hepatocellular carcinomas in a study in which rainbow trout (*Oncorhynchus mykiss*) received 3, 200, 400, or 800

mg NDMA/kg in the diet over 52 weeks. Tumours did not form in trout receiving 3 mg/kg, although body weight was reduced. OME (1998) observed that growth reduction in rainbow trout was a more sensitive response than tumour induction.

Frogs (*Rana temporaria*) were exposed to 5 mg NDMA/litre in water for 63 days and 203 days. In both studies, the frogs developed hepatocellular carcinomas as well as adenomas and tumours of the haematopoietic system. Approximately 44% of the frogs exposed for 203 days developed tumours (Khudoley, 1977). In another species of frog (*Xenopus borealis*) exposed for 52 weeks to 400 mg NDMA/litre in aquarium water, 54% of the test animals developed liver and kidney tumours (Khudoley & Picard, 1980). The authors believed that amphibians were more sensitive (shorter latency period and higher tumour incidence) than fish to the carcinogenic effects of the nitrosamine.

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification

Although NDMA is acutely toxic and induces hepatic damage in several species at dose levels of approximately 1 mg/kg body weight per day in short-term experiments, the main concern is its carcinogenicity: NDMA has been consistently shown to be a potent carcinogen in all experimental species studied. Data on other end-points are very limited.

Available data are consistent with the toxicological effects of NDMA being due, in large part, to the alkylation of biological macromolecules (e.g., DNA, RNA, proteins) by the methyldiazonium ion formed during metabolism. Putative pathways for the metabolism of NDMA are similar in rodents and humans.

11.1.1.1 Carcinogenicity

Information relevant to assessment of the carcinogenicity of NDMA has been derived from epidemiological (case-control) studies of the general population, carcinogenesis bioassays involving laboratory animals, and supporting data related to the genotoxicity, metabolism, and interaction of this compound with biological macromolecules.

Although the database is rather limited, data from epidemiological studies are at least suggestive of an

¹ The RRs (95% CIs) (adjusted for age, sex, municipality, smoking, and energy intake) of colorectal cancer among those with intakes of NDMA in the first (reference), second, third, and fourth quartiles were 1, 1.47 (0.69–3.11), 1.95 (0.95–3.99), and 2.12 (1.04–4.33), respectively (*P* = 0.47 for trend).

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association between exposure to NDMA and several forms of cancer (i.e., gastric and lung), with some consistency of evidence for gastric cancer and for exposure–response for lung cancer, the latter in studies in which matching or control for confounders was most extensive. Although estimated intakes in these investigations were based on dietary recall, and although confounding factors such as alcohol were not accounted for, the data fulfil, at least in part, some of the traditional criteria for causality of an association between ingestion of NDMA and cancer.

With the exception of a very extensive recent study, the identified carcinogenesis bioassays for NDMA are considered limited by current standards (e.g., single dose levels, small group sizes, limited histopathological examination). The weight of evidence of the carcinogenicity of NDMA in mammalian species is consistent and convincing. Moreover, the pattern of tumour development is characteristic of that for a mode of action of carcinogenesis involving direct interaction with genetic material. In available studies, NDMA has induced tumours in all species examined (mice, rats, hamsters), at relatively low doses in some cases, irrespective of the route of exposure (oral, inhalation); tumours were induced in a wide range of tissues, including the liver, Leydig cells, lungs, kidney, and nasal cavity, in the absence of significant non-neoplastic effects, in the limited number of studies in which these were well examined. Where it was reported, time to first tumour was relatively short. The incidence of specific tumours has been increased following administration of even a single dose or repeated doses for short periods (i.e., 2–3 weeks); tumours have also been observed in the offspring of exposed pregnant rats and mice.

NDMA has been consistently mutagenic and clastogenic in human and rodent cells exposed *in vitro*. Clear evidence of genetic effects has also been observed in a number of tissues from animals exposed to this substance. Notably, genotoxic effects have been observed in tissues (i.e., liver, kidney, lung) where tumours commonly arise following experimental exposure to NDMA and in germ cells.

DNA adducts (in particular, *O*⁶-methylguanine) formed by the methyl diazonium ion generated during metabolism likely play a critical role in NDMA carcinogenicity. Observed variations in carcinogenicity among species and strains correlate well with variations in activity of *O*⁶-methylguanine DNA-methyltransferase. Putative pathways for the metabolism of NDMA are similar in rodents and humans, and indeed the formation of *O*⁶-methylguanine has been detected in human tissues exposed to NDMA.

Therefore, owing to the considerable evidence of carcinogenicity of NDMA in laboratory species, evidence of direct interaction with DNA consistent with tumour formation, and the apparent lack of qualitative species-specific differences in the metabolism of this substance, NDMA is highly likely to be carcinogenic to humans.

11.1.1.2 Non-neoplastic effects

Information on adverse health effects other than cancer in humans associated with exposure to NDMA is limited. In case reports, liver failure, brain haemorrhage, and death have been attributed to the ingestion of NDMA. Effects resulting from exposure to unspecified amounts of airborne NDMA have included an enlarged liver and spleen, hepatic cirrhosis, jaundice, ascites, and death.

Data on non-neoplastic effects in laboratory animals associated with exposure to NDMA are also inadequate, attributable primarily to the focus on its carcinogenicity. Effects on the liver and kidney in repeated-dose toxicity studies (>0.2 mg NDMA/kg body weight per day), embryo toxicity and embryo lethality in single-dose developmental studies (20–30 mg/kg body weight), and a range of immunological effects (suppression of humoral- and cell-mediated immunity) reversible at lowest concentrations (5 mg NDMA/litre) have been reported.

11.1.2 Dose–response analyses

The principal route of human exposure to NDMA for the general population, including those exposed in the vicinity of point sources, is ingestion.¹ Moreover, information on exposure–response for the critical end-point following inhalation and dermal exposure to NDMA is limited. Therefore, quantitation of dose–response is limited here to exposure via ingestion.

Scaling for variations in the ratios of surface area to body weight between rodent species and humans was not considered appropriate for the measures of exposure–response developed on the basis of experimental data in animals, since it is highly probable that the carcinogenicity of NDMA is mediated primarily through the generation of an active metabolite (i.e., the methyl diazonium ion).

¹ Estimated exposure would be higher if the population is assumed to be exposed continuously to the maximum concentration of NDMA in indoor air (see Table 2).

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11.1.2.1 Carcinogenicity

Cancer is clearly the critical end-point for quantitation of exposure–response for risk characterization of NDMA. This has been the best characterized end-point for this substance. Moreover, in general, tumours occur at lowest concentration, compared with those typically reported to induce non-cancer effects. An increased incidence of hepatic tumours was observed at doses as low as approximately 0.1 mg/kg body weight per day in rats (Brantom, 1983; Peto et al., 1991a,b), and the genotoxicity of NDMA (including formation of putatively critical adducts with DNA), for which the weight of evidence is exceedingly consistent and convincing, undoubtedly plays a critical role in tumour induction. A 2-fold increase in stillbirths and neonatal deaths (combined) was observed in mice receiving an estimated daily intake of 0.02 mg NDMA/kg body weight per day for 75 days prior to mating and throughout pregnancy and lactation. However, exposure to NDMA had no effect upon maternal fluid consumption, litter size, or average body weight of the weanlings, and there were no consistent gross or histopathological abnormalities in the stillborn fetuses or dead neonates to account for the increased mortality. Moreover, increased mortality was not observed in another study in which mice were administered higher doses of the nitrosamine (i.e., a single intraperitoneal injection of 7.4 mg NDMA/kg body weight on day 16 or 19 of gestation) (Anderson et al., 1989).

Quantitation of exposure–response for cancer for NDMA is based on studies in laboratory animals, since existing epidemiological data, although suggestive of a possible association between ingestion of NDMA and cancer, are inadequate to serve as a basis for characterization of exposure–response. There appear to be no *qualitative* differences in metabolism of NDMA between humans and laboratory animals, and there is no reason to believe that humans would respond qualitatively differently.

By far the most suitable study for exposure–response analyses of the carcinogenic effects of NDMA is that reported by Brantom (1983) and Peto et al. (1991a,b), which involved the administration of NDMA in drinking-water to a large number ($n = 15$) of large dose groups ($n = 60$) of male and female rats. Other available bioassays are considerably more limited — i.e., single dose groups, small group sizes, and histopathological examination often restricted to one tissue.

Quantitation of exposure–response for cancer involved calculation of the tumorigenic dose₀₅ (TD₀₅; i.e., the dose level that causes a 5% increase in tumour

incidence over background).¹ The lowest TD₀₅ was 34 µg/kg body weight per day for the development of biliary cystadenomas in female rats. This equates to a unit risk of 1.5×10^{-3} per µg/kg body weight (i.e., 0.05/34).

11.1.2.2 Non-neoplastic effects

Information on non-neoplastic effects in humans and experimental animals associated with exposure to NDMA is inadequate to characterize exposure–response.

Effects on the liver (i.e., hepatocyte vacuolization, portal venopathy, and necrosis/haemorrhage) and kidney (i.e., glomerulus dilatation and slight thickening of the Bowman's capsule), “congestion” in the spleen and lungs, and gastrointestinal haemorrhage have been reported in short- and medium-term studies of animals receiving greater than 0.2 mg NDMA/kg body weight per day. Embryo toxicity and embryo lethality have been observed in a number of inadequately reported studies of often non-standard protocol following oral exposure to high (maternally toxic) doses in the range of 20–30 mg/kg body weight per day or lower doses upon repeated exposure (1.4–2.9 mg/kg body weight per day by gavage or 5 mg/kg body weight per day in diet); teratogenicity has not been reported. In one report of a single-generation study (Anderson et al., 1978) in mice, the number of stillbirths and neonatal deaths (combined) was increased 2-fold at 0.1 mg/litre (estimated daily intake of 0.02 mg NDMA/kg body weight per day). However, confidence in the significance of this observation is mitigated by the lack of a more reliable estimate of intake, the absence of significant effects on other reproductive parameters, the lack of histopathological changes to account for the increased mortality, as well as the observation of no increased fetal mortality in dams administered a higher total dose of NDMA (Anderson et al., 1989).

Although suppression of cell- and humoral-mediated immune responses was reported in mice consuming doses greater than approximately 1 mg/kg body weight per day in drinking-water for 30–120 days, effects were fully reversible within 30 days of cessation of exposure.

Based on available documented studies, therefore, non-neoplastic effects of NDMA, where they have been observed, have typically occurred (except for one report of the single-generation reproduction study) at doses greater than those at which increases in tumour incidence have been reported in other studies (i.e., the

¹ Additional information on calculation of the TD₀₅ is presented in Appendix 4.

latter was observed at doses as low as about 0.1 mg/kg body weight per day in rats). In addition, in view of the likely critical role of the genotoxicity of NDMA in the induction of tumours, for which the weight of evidence is consistent and convincing, cancer is clearly the critical end-point for quantitation of exposure–response for risk characterization. Measures based on this end-point will be protective for other reported non-neoplastic effects.

11.1.3 Sample risk characterization

For substances such as NDMA, for which it is likely that the mode of action for the induction of tumours involves direct interaction with genetic material, quantitative estimates of carcinogenic potency (i.e., the TD₀₅) may be compared with estimates of exposure to characterize risk. In the sample country (Canada), with the exception of monitoring of NDMA in water supplies in Ontario, most of the sampling and analyses for this contaminant in the general environment have been source directed — i.e., confined to foodstuffs in which it is most likely to be present or media in the vicinity of industrial sources.¹ The margins between the lowest value for the TD₀₅ (i.e., 34 µg/kg body weight per day) and the highest reasonable worst-case estimates for the intake of NDMA by individuals in Canada (see Table 2) — that is, for children (0.5–4 years) with intakes from air, water, and food (0.029 µg/kg body weight per day), for children (0.5–4 years) exposed to ETS-contaminated indoor air (0.13 µg/kg body weight per day), or for infants (0–0.5 years) consuming contaminated ground-water (0.31 µg/kg body weight per day) — are low (approximately 1170, 260, and 110, respectively), equating to low dose risks of >10⁻⁵. Risks for ambient drinking-water are between 10⁻⁷ and 10⁻⁵. It should be noted that the estimates of intake from food representative of the situation today are probably lower, due to the impact of subsequent introduction of changes in food processing and controls to limit the formation of NDMA. NDMA is a genotoxic carcinogen, and exposure should be reduced to the extent possible.

11.1.4 Uncertainties and degree of confidence in human health risk characterization

Non-neoplastic effects associated with exposure to NDMA have not been well studied. Although non-neoplastic effects in laboratory animals have typically been observed only at dose levels higher than those associated with increased tumour incidence (approximately 0.1 mg/kg body weight per day in rats), in one report, stillborn and neonatal deaths (combined) were observed in a single-generation study in mice receiving

an estimated intake of approximately 0.02 mg/kg body weight per day for 75 days. While there is uncertainty surrounding the biological significance of this finding, further experimental work in this area would provide more definitive information concerning potential reproductive effects linked to long-term exposure to low levels of NDMA.

There is a high degree of certainty that the genotoxicity of NDMA (likely involving the formation of O⁶-methylguanine in DNA) is critical in the mechanism of carcinogenicity of this substance. Also, due to the unusually large number of dose groups in the critical study, characterization of exposure–response for induction of tumours by NDMA in laboratory animals is considered to be optimal.

Comparison of the highest TD₀₅ identified from the study in which exposure–response was best characterized (i.e., 82 µg/kg body weight per day for hepatic carcinomas in female rats) with the highest reasonable worst-case estimates for the intake of NDMA by individuals in Canada (in section 11.1.3) would yield margins approximately 2.4-fold (i.e., 82 µg/kg body weight per day ÷ 34 µg/kg body weight per day) higher than those derived (section 11.1.3) on the basis of the hepatic biliary cystadenomas in female rats.

11.2 Evaluation of environmental effects

11.2.1 Terrestrial assessment end-points

Since NDMA is not persistent in the environment, environmental effects are most likely to occur near point sources. Results of various industry and municipal surveys indicate that most releases of NDMA are to water. When NDMA is released to water, nearly all of it remains and reacts in the water phase. Based on the short half-life of NDMA in air and the amounts being released to air, it is unlikely that effects will occur on wildlife near point sources. Since there are no detectable releases to sediment and soil, and as NDMA does not move from water to these compartments, effects on wildlife do not appear to be of concern. Therefore, the assessment of NDMA released to water focuses on organisms exposed in water near point sources.

11.2.2 Aquatic assessment end-points

Assessment end-points include abundance and survival of fish, invertebrates, amphibians, and algae. These organisms are an integral part of ecosystems, as each trophic level provides food for higher levels in the aquatic food-chain. For example, algae are primary producers, forming the base of the food-chain. The abundance and productivity of phytoplankton are important to aquatic ecosystems, because phytoplankton provides

¹ NDMA was not detected in a single survey of ambient air not impacted by point sources.

food for a variety of planktivorous organisms and thus controls energy flow in a portion of the ecosystem. Cladocerans such as *Daphnia magna* consume bacteria and phytoplankton and are themselves consumed by many fish species. Various fish species feed on aquatic vegetation, phytoplankton, zooplankton, benthic invertebrates, benthic vertebrates, etc. Vertebrate omnivores provide food for vertebrate carnivores. The most sensitive measurement end-point identified for aquatic species was growth of the green alga (*Selenastrum capricornutum*).

As NDMA is a potent inducer of acute toxic and chronic neoplastic lesions in aquatic species, assessment end-points reflecting these effects are mentioned here. In nearly all of the studies conducted on a variety of species at different trophic levels, tumours have resulted from exposure to NDMA. Although a tumorigenic end-point is not traditionally used as an indicator of a population-level effect, it may have implications if an endangered species is found in the area of discharge of effluent containing NDMA. At this time, however, implications of tumour induction in environmental species are unclear.

11.2.3 Sample environmental risk characterization

11.2.3.1 Aquatic organisms

Based on the sources and fate of NDMA, and because data on concentrations in ambient water near point sources are not available, end-of-pipe concentrations in final effluent were used as a measure of exposure of aquatic organisms. Recent concentrations have been selected to reflect present exposures. The highest concentration of NDMA in wastewater discharged to a water body was 0.266 µg/litre. Although this concentration is expected to decrease, as the company installed a wastewater treatment plant in 1998, this value is used as the estimated exposure value (EEV) in the hyperconservative analysis of long-term exposure for aquatic plants and animals.

For long-term exposure of aquatic organisms to NDMA, the critical toxicity value (CTV) is 4000 µg/litre, based on a 13-day EC₅₀ for inhibition of growth in the green alga (*Selenastrum capricornutum*). This value was selected from a data set composed of several studies conducted on at least eight species of aquatic organisms, which include phytoplankton, zooplankton, fish, amphibians, and invertebrates. It is important to note that in the second most sensitive study, tumours were present in the organism. Khudoley (1977) reported that liver tumours were induced in 44% of frogs (*Rana temporaria*) after 203 days of exposure at a concentration of 5000 µg/litre. Again, as was indicated in

section 11.2.2, the implications of tumour induction as a population-level effect cannot be determined at this time.

For a hyperconservative analysis, the estimated no-effects value (ENEV) is derived by dividing the CTV by an application factor of 100. This accounts for the uncertainty surrounding the conversion of a short-term EC₅₀ to a chronic no-effects value, the extrapolation from laboratory to field conditions, and interspecies and intra-species variations in sensitivity. As a result, the ENEV is 40 µg/litre.

The hyperconservative quotient is calculated by dividing the EEV of 0.266 µg/litre by the ENEV for green algae as follows:

$$\begin{aligned}\text{Quotient} &= \frac{\text{EEV}}{\text{ENEV}} \\ &= \frac{0.266 \mu\text{g/litre}}{40 \mu\text{g/litre}} \\ &= 0.007\end{aligned}$$

Since the hyperconservative quotient is less than one, it is unlikely that NDMA releases will cause adverse effects on populations of aquatic organisms in the sample country.

11.2.4 Discussion of uncertainty

Regarding effects of NDMA on aquatic organisms, there is uncertainty in the extrapolation from available toxicity data to potential ecosystem effects. The toxicity data set for aquatic biota, however, is considered adequate, as it includes a variety of species from different trophic levels. While some of the studies are relatively old (1960s–1980s), they are generally of good quality and are considered acceptable for the assessment.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

NDMA has been classified by the International Agency for Research on Cancer (IARC, 1987) as a “probable human carcinogen (Group 2A),” based upon sufficient evidence of a carcinogenic effect in experimental animal species and the demonstrated similarities in its metabolism by human and rodent tissues.

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APPENDIX 1 — SOURCE DOCUMENT**Environment Canada & Health Canada (2001)**

Copies of the *Canadian Environmental Protection Act* Priority Substances List assessment report (Environment Canada & Health Canada, 2001) and unpublished supporting documentation for NDMA may be obtained from:

Commercial Chemicals Evaluation Branch
Environment Canada
14th floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
Canada K1A 0H3

or

Environmental Health Centre
Health Canada
Address Locator: 0801A
Tunney's Pasture
Ottawa, Ontario
Canada K1A 0L2

Initial drafts of the supporting documentation and assessment report for NDMA were prepared by staff of Health Canada and Environment Canada. H. Hirtle contributed additional information in the preparation of the draft CICAD.

Environmental sections of the assessment report were reviewed externally by J. Ballantine (Health Canada), A. McLarty (Ontario Ministry of the Environment), E. McBean and J. Kochany (Conestoga-Rovers & Associates), and D. Carlisle (Brez-Carlisle Inc.).

In order to address primarily adequacy of coverage, sections of the supporting documentation pertaining to human health were reviewed externally by B. Birmingham (Ontario Ministry of the Environment) and R. Brecher (Globaltox International Consultants, Inc.).

Accuracy of reporting, adequacy of coverage, and defensibility of conclusions with respect to hazard characterization and dose-response analysis were considered at a panel meeting of the following members, convened by Toxicology Excellence for Risk Assessment (TERA) on 12 August 1999 in Ottawa, Ontario:

M. Bogdanffy, DuPont Haskell Laboratory
J. Christopher, California Environmental Protection Agency
M. Dourson, TERA
S. Felter, Procter & Gamble
J. Mandel, Exponent
R. Rudel, Silent Spring Institute
V. Walker, New York State Department of Health

APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on NDMA was sent for review to institutions and organizations identified by IPCS after contact with IPCS national contact points and Participating Institutions, as well as to identified experts. Comments were received from:

A. Aitio, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

M. Baril, International Programme on Chemical Safety/ Institut de Recherche en Santé et en Sécurité du Travail du Québec, Montreal, Quebec, Canada

R. Benson, Drinking Water Program, US Environmental Protection Agency, Denver, CO, USA

R. Cary, Health and Safety Executive, Bootle, Merseyside, United Kingdom

R. Chhabra, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, USA

C. Elliott-Minty, Health and Safety Executive, Bootle, Merseyside, United Kingdom

E. Frantik, National Institute of Public Health, Center of Industrial Hygiene and Occupational Diseases, Praha, Czech Republic

R. Hertel, Federal Institute for Health Protection of Consumers and Veterinary Medicine, Berlin, Germany

T.G. Hrnsi, National Institute of Public Health, Oslo, Norway

A.P. Hugenholtz, Bureau of Chemical Safety, Health Canada, Ottawa, Ontario, Canada

E. Srdlerlund, National Institute of Public Health, Oslo, Norway

U. Steinus, Karolinska Institute, Stockholm, Sweden

Y.-W. Stevens, Agency for Toxic Substances and Disease Registry, Atlanta, GA, USA

K. Ziegler-Skylakakis, Commission of the European Communities/European Union, Luxembourg

APPENDIX 3 — CICAD FINAL REVIEW BOARD

Utrecht, Utrecht, The Netherlands

Geneva, Switzerland, 8–12 January 2001

Members

Dr A.E. Ahmed, Molecular Toxicology Laboratory, Department of Pathology, University of Texas Medical Branch, Galveston, TX, USA

Mr R. Cary, Health and Safety Executive, Merseyside, United Kingdom (*Chairperson*)

Dr R.S. Chhabra, General Toxicology Group, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, USA

Dr S. Czerczak, Department of Scientific Information, Nofer Institute of Occupational Medicine, Lodz, Poland

Dr S. Dobson, Centre for Ecology and Hydrology, Cambridgeshire, United Kingdom

Dr O.M. Faroon, Division of Toxicology, Agency for Toxic Substances and Disease Registry, Atlanta, GA, USA

Dr H. Gibb, National Center for Environmental Assessment, US Environmental Protection Agency, Washington, DC, USA

Dr R.F. Hertel, Federal Institute for Health Protection of Consumers and Veterinary Medicine, Berlin, Germany

Dr A. Hirose, Division of Risk Assessment, National Institute of Health Sciences, Tokyo, Japan

Dr P.D. Howe, Centre for Ecology and Hydrology, Cambridgeshire, United Kingdom (*Rapporteur*)

Dr D. Lison, Industrial Toxicology and Occupational Medicine Unit, Université Catholique de Louvain, Brussels, Belgium

Dr R. Liteplo, Existing Substances Division, Bureau of Chemical Hazards, Health Canada, Ottawa, Ontario, Canada

Dr I. Mangelsdorf, Chemical Risk Assessment, Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Germany

Ms M.E. Meek, Existing Substances Division, Safe Environments Program, Health Canada, Ottawa, Ontario, Canada (*Vice-Chairperson*)

Dr S. Osterman-Golkar, Department of Molecular Genome Research, Stockholm University, Stockholm, Sweden

Dr J. Sekizawa, Division of Chem-Bio Informatics, National Institute of Health Sciences, Tokyo, Japan

Dr S. Soliman, Department of Pesticide Chemistry, Faculty of Agriculture, Alexandria University, El-Shatby, Alexandria, Egypt

Dr M. Sweeney, Education and Information Division, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

Professor M. van den Berg, Environmental Sciences and Toxicology, Institute for Risk Assessment Sciences, University of

Observers

Dr W.F. ten Berge, DSM Corporate Safety and Environment, Heerlen, The Netherlands

Dr K. Ziegler-Skylakakis, Commission of the European Communities, Luxembourg

Secretariat

Dr A. Aitio, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr Y. Hayashi, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr P.G. Jenkins, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr M. Younes, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

APPENDIX 4 — CALCULATION OF TUMORIGENIC DOSE₀₅

The tumorigenic dose₀₅ (TD₀₅; i.e., the dose level that causes a 5% increase in tumour incidence over background) was calculated by first fitting the multistage model to the dose–response data. The multistage model is given by

$$P(d) = 1 - e^{-q_0 - q_1 d - \dots - q_k d^k}$$

where d is dose, k is the number of dose groups in the study minus one, $P(d)$ is the probability of the animal developing a tumour at dose d , and $q_i > 0$, $i = 1, \dots, k$ are parameters to be estimated. TD₀₅s were then calculated as the dose D that satisfies

$$\frac{P(D) - P(0)}{1 - P(0)} = 0.05$$

A chi-square lack of fit test was performed for each of the three tumour types. The degrees of freedom for this test are equal to k minus the number of q_i 's for which estimates are non-zero. A P -value less than 0.05 indicates a significant lack of fit.

The study reported by Brantom (1983) and Peto et al. (1991a,b) contained 15 dose groups and controls, which is unusually large. Upper dose groups for which there was downturn in the dose–response curve were first eliminated from calculations of the TD₀₅. These dose groups add no information to the shape of the dose–response curve in the range of the TD₀₅ and contribute to lack of fit of the model. In addition, extreme downturn is likely a sign that animals are dying of some other cause before having a chance to develop the tumour of interest.

Two methods were used to fit models to the large number

of dose groups. In the first method, quadratic models (i.e., models with $k = 2$) were fit to the full set of data, less any dose groups contributing to downturn at the upper end of the dose–response curve. Any model with k larger than 2 did not converge when fitting models to the full data set. The second method involved reducing the number of dose groups to 10 (or less) by first eliminating upper dose groups with downturn and then collapsing adjacent similar dose groups together. Collapsing was accomplished by averaging the dose level and totalling the number of tumours for the two groups. Global82 (Howe & Crump, 1982) was then used to fit full multistage models to the reduced data. With the exception of biliary cystadenomas in females, these models did not show significant lack of fit. However, they generally appeared to overestimate the risk in the range of the TD₀₅, resulting in TD₀₅ values that might be overly conservative. There was no evidence of a dose–response relationship for haemangiosarcomas in females; these data were not modelled, therefore, for the purpose of calculating a TD₀₅.

After reducing the data to 10 dose groups, the multistage model still occasionally exhibited lack of fit, due in large part to a levelling off of the dose–response relationship at higher doses. Since a good fit in the range of the TD₀₅ is required, upper dose groups were systematically eliminated until a reasonable fit was achieved. The data finally used to compute TD₀₅s for hepatic tumours in the male and female rats from the Brantom (1983) and Peto et al. (1991a,b) study are presented in Tables A-1 and A-2.

After comparing the two methods of model fitting, the second was judged to provide a better description of the dose–response relationship in the range of the TD₀₅. These fits were used to generate the final TD₀₅s. The TD₀₅s and model-fitting information are presented in Table A-3 and Figure A-1.

Table A-1: Data on hepatic carcinogenicity in male rats used for modelling.

Carcinoma		Haemangiosarcoma		Biliary cystadenoma	
Intake (mg/kg body weight per day)	Incidence	Intake (mg/kg body weight per day)	Incidence	Intake (mg/kg body weight per day)	Incidence
0	2/192	0	2/192	0	2/192
0.0020	2/96	0.002	0/96	0.0020	4/96
0.0080	3/96	0.005	1/48	0.0080	4/96
0.0330	4/96	0.011	2/48	0.0330	2/96
0.0760	11/96	0.022	0/48	0.0760	10/96
0.1200	26/96	0.044	1/48	0.1200	24/96
0.1960	44/96	0.065	1/48	0.1960	26/96
0.3045	66/96	0.087	6/48	0.3045	33/96
		0.109	6/48		
		0.131	14/48		

Table A-2: Data on hepatic carcinogenicity in female rats used for modelling.

Carcinoma		Biliary cystadenoma	
Intake (mg/kg body weight per day)	Incidence	Intake (mg/kg body weight per day)	Incidence
0	2/192	0	4/192
0.0035	0/96	0.002	1/48
0.0145	4/96	0.005	4/48
0.057	8/96	0.010	0/48
0.134	10/96	0.019	3/48
0.210	10/96	0.038	5/48
0.344	19/96	0.076	7/48
0.459	18/48	0.115	34/48
0.612	33/48		

Table A-3: TD₀₅s for NDMA.

	TD ₀₅ (µg/kg body weight per day)	95% lower confidence limit on TD ₀₅	Chi-square	df	P-value
Male rats					
Hepatic carcinoma	38	24	2.17	5	0.82
Hepatic haemangiosarcoma	78	48	7.67	6	0.26
Hepatic biliary cystadenoma	35	29	10.25	6	0.11
Female rats					
Hepatic carcinoma	82	61	7.36	5	0.19
Hepatic biliary cystadenoma	34	18	7.036	5	0.22

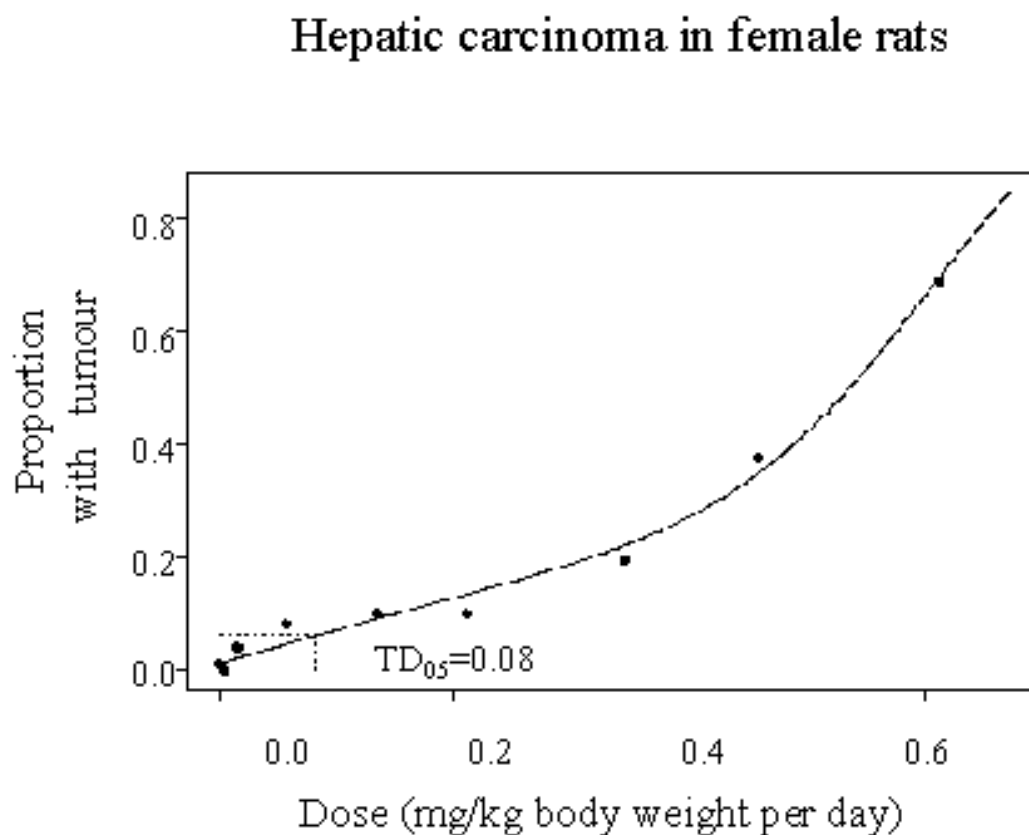
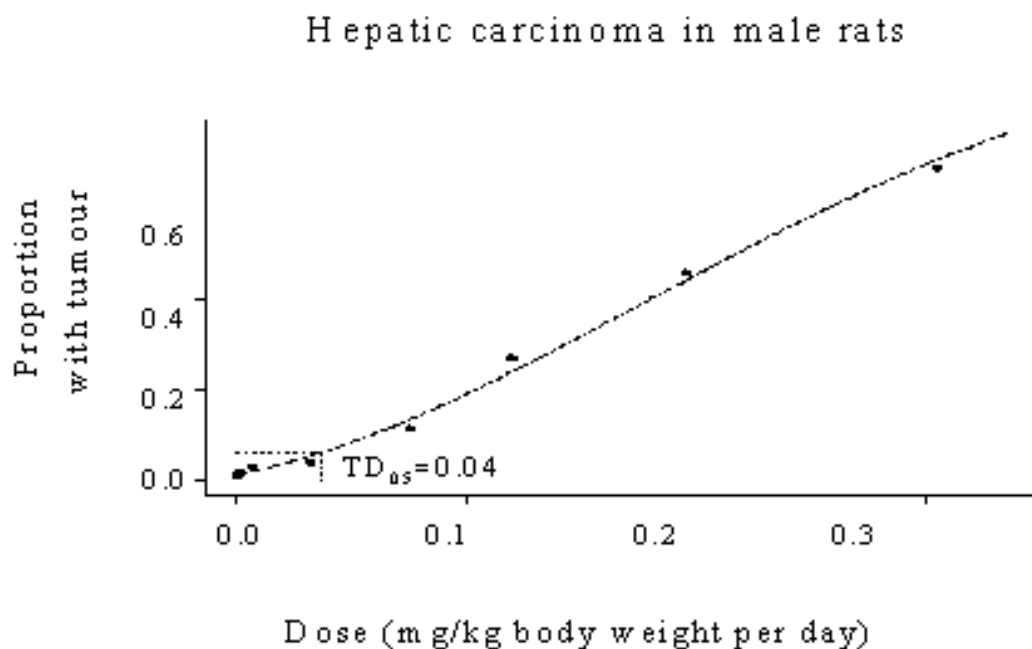
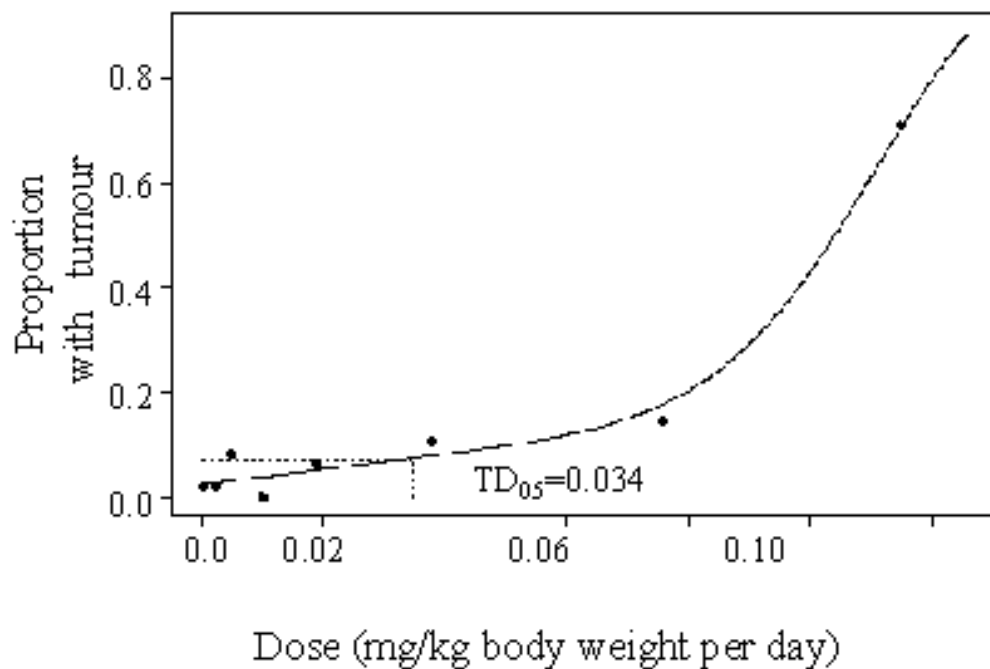


Figure A-1: TD_{05} for NDMA.

Biliary cystadenoma in female rats



Biliary cystadenoma in male rats

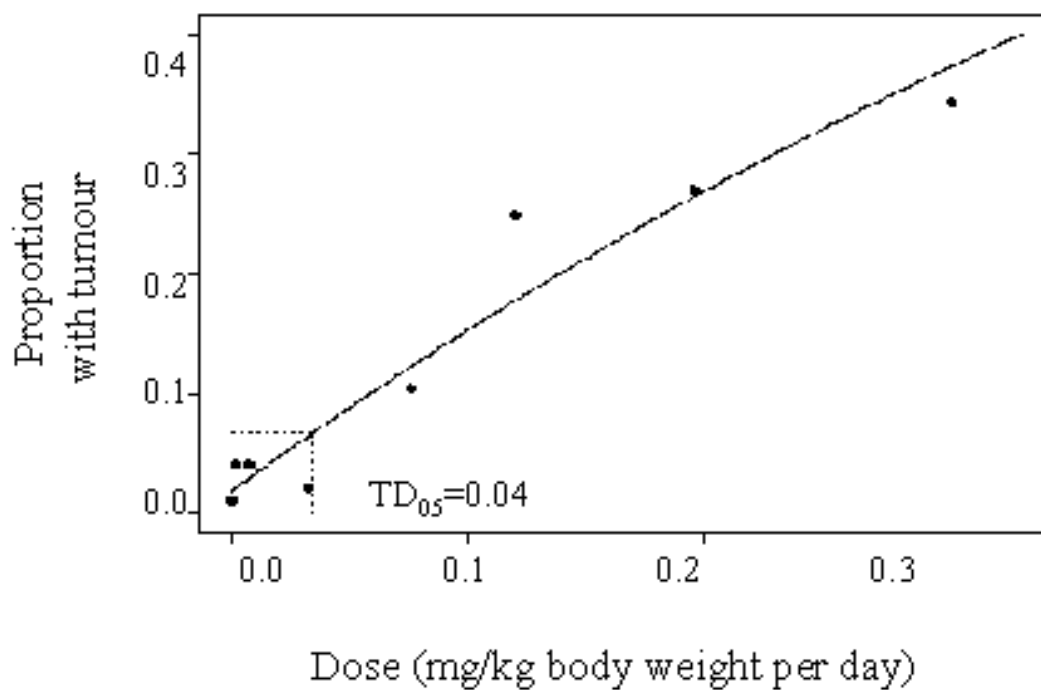


Figure A-1: TD₀₅s for NDMA.

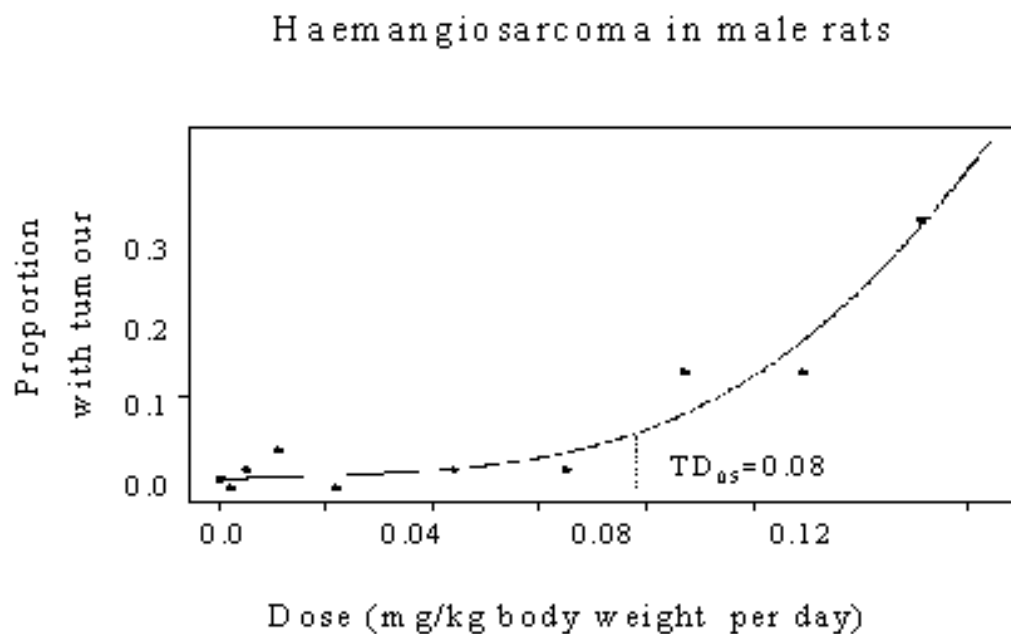


Figure A-1: TD_{05} for NDMA.

CAS No: 62-75-9
RTECS No: IQ0525000
UN No: 2810
EC No: 612-077-00-3

Dimethylnitrosamine
N-Methyl-N-nitrosomethylamine
DMN
 $C_2H_6N_2O / (CH_3)_2NN=O$
Molecular mass: 74.1

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Combustible.	NO open flames.	Powder, carbon dioxide.
EXPLOSION			

EXPOSURE		AVOID ALL CONTACT!	IN ALL CASES CONSULT A DOCTOR!
Inhalation	Sore throat. Cough. Nausea. Diarrhoea. Vomiting. Headache. Weakness.	Ventilation, local exhaust, or breathing protection.	Fresh air, rest. Refer for medical attention.
Skin	Redness. Pain.	Protective gloves.	Remove contaminated clothes. Rinse skin with plenty of water or shower.
Eyes	Pain. Redness.	Face shield, or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Abdominal cramps. (Further see Inhalation).	Do not eat, drink, or smoke during work. Wash hands before eating.	Give a slurry of activated charcoal in water to drink. Induce vomiting (ONLY IN CONSCIOUS PERSONS!). Refer for medical attention.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Evacuate danger area! Collect leaking and spilled liquid in sealable containers as far as possible. Absorb remaining liquid in sand or inert absorbent and remove to safe place. Chemical protection suit including self-contained breathing apparatus.	T+ Symbol N Symbol R: 45-25-26-48/25-51/53 S: 53-45-61 Note: E UN Hazard Class: 6.1 UN Pack Group: I Do not transport with food and feedstuffs. Unbreakable packaging; put breakable packaging into closed unbreakable container.

EMERGENCY RESPONSE	STORAGE
Transport Emergency Card: TEC (R)-61G61b	Separated from strong oxidants, food and feedstuffs. Cool. Keep in the dark. Well closed.

IMPORTANT DATA

Physical State; Appearance
 YELLOW OILY LIQUID

Chemical dangers

The substance decomposes on heating producing nitrogen oxides. Reacts with strong oxidants and strong bases.

Occupational exposure limits

TLV: A3, skin (ACGIH 2000).
 MAK: Class 2 (2000)

Routes of exposure

The substance can be absorbed into the body by inhalation and by ingestion.

Inhalation risk

No indication can be given about the rate in which a harmful concentration in the air is reached on evaporation of this substance at 20°C.

Effects of short-term exposure

The substance is irritating to the eyes, the skin and the respiratory tract. The substance may cause effects on the liver, resulting in jaundice. The effects may be delayed. See Notes. Medical observation is indicated.

Effects of long-term or repeated exposure

The substance may have effects on the liver, resulting in liver function impairment and cirrhosis. This substance is probably carcinogenic to humans.

PHYSICAL PROPERTIES

Boiling point: 151°C
 Relative density (water = 1): 1.0
 Solubility in water: very good
 Vapour pressure, Pa at 20°C: 360

Relative vapour density (air = 1): 2.56
 Flash point: 61°C
 Octanol/water partition coefficient as log Pow: -0.57

ENVIRONMENTAL DATA

NOTES

The symptoms of jaundice do not become manifest until some hours have passed. Environmental effects from the substance have not been investigated adequately.

ADDITIONAL INFORMATION

LEGAL NOTICE

Neither the EC nor the IPCS nor any person acting on behalf of the EC or the IPCS is responsible for the use which might be made of this information

RÉSUMÉ D'ORIENTATION

Ce CICAD relatif à la *N*-nitrosodiméthylamine (NDMA) a été préparé conjointement par la Direction de l'Hygiène du Milieu de Santé Canada et la Direction de l'Évaluation des produits chimiques commerciaux d'Environnement Canada à partir d'une documentation rédigée simultanément dans le cadre du programme sur les substances prioritaires prévu par la *Loi canadienne sur la protection de l'environnement* (LCPE). Les études sur les substances prioritaires prescrites par la LCPE ont pour objectif d'évaluer les effets potentiels sur la santé humaine d'une exposition indirecte à celles de ces substances qui sont présentes dans l'environnement ainsi que leurs effets sur l'environnement lui-même. Bien que l'exposition professionnelle n'ait pas été le sujet du document initial (Environnement Canada & Santé Canada, 2001), des données sur la question ont été incluses dans le présent CICAD. La présente mise au point prend en compte les données publiées jusqu'en août 1999 en ce qui concerne les effets sanitaires et jusqu'à fin août 1998 en ce qui concerne les effets sur l'environnement.¹ D'autres mises au point ont été également consultées, à savoir celles du CIRC (1978), de l'OME (1991, 1998) et de la BIBRA Toxicology International (1997, 1998). Des renseignements sur la nature de l'examen par des pairs et la disponibilité du document de base sont donnés à l'appendice 1. Les informations concernant l'examen par des pairs du présent CICAD figurent à l'appendice 2. Ce CICAD a été approuvé en tant qu'évaluation internationale lors d'une réunion du Comité d'évaluation finale qui s'est tenue à Genève (Suisse), du 8 au 12 janvier 2001. La liste des participants à cette réunion se trouve à l'appendice 3. La fiche internationale sur la sécurité chimique de la NDMA (ICSC 0525), préparée par le Programme international sur la sécurité chimique (IPCS, 1993), est également reproduite dans le présent document.

La *N*-nitrosodiméthylamine (NDMA) est la plus simple des dialkylnitrosamines. Bien que n'étant plus utilisée dans l'industrie ou le commerce ni au Canada, ni

aux États-Unis, elle continue néanmoins d'être libérée dans l'environnement comme sous-produit ou contaminant par diverses installations industrielles et par les stations municipales de traitement des eaux usées. Ce sont les usines de pesticides, de pneumatiques, de colorants et les unités de production d'alkylamines qui en rejettent le plus. De la NDMA peut également se former dans les conditions naturelles dans l'air, l'eau et le sol par suite de certains processus chimiques, photochimiques ou biologiques et on en a mis en évidence dans l'eau de boisson et dans les gaz d'échappement des automobiles.

C'est principalement par photolyse que la NDMA s'élimine des eaux de surface, de l'atmosphère et du sol. Toutefois, dans les eaux superficielles riches en substances organiques et matières en suspension, la photodécomposition est très ralentie. Dans les eaux des nappes phréatiques et dans le sol, c'est la biodégradation qui constitue la voie d'élimination prédominante. La NDMA a vraisemblablement peu de chances d'être transportée sur de longues distances ou de se répartir dans le sol et les sédiments. En raison de sa solubilité et de la faible valeur de son coefficient de partage, la NDMA a la possibilité de passer par lessivage dans les eaux souterraines et de s'y maintenir. Elle subit une métabolisation et ne s'accumule pas. Elle n'est pas présente en quantités décelables dans les eaux de surface, sauf en cas de contamination localisée aux alentours de sites industriels, où l'on a pu mesurer des concentrations allant jusqu'à 0,266 µg par litre au débouché de certains émissaires.

Selon des enquêtes limitées effectuées dans le pays sur lequel on s'est basé pour caractériser le risque type (le Canada), la NDMA n'est pas décelable dans l'air ambiant, sauf à proximité de sites industriels. En revanche, de faibles concentrations de NDMA - provenant de stations de traitement ou d'eaux souterraines contaminées par des effluents industriels - ont été mesurées dans de l'eau de consommation. On a également mis en évidence la présence de NDMA dans diverses denrées alimentaires, le plus souvent dans de la bière, des salaisons ou des fumaisons, des produits pisciaires et dans certains fromages avec, il est vrai, une diminution de la concentration ces dernières années en raison d'un changement dans le mode de traitement de ces produits. Le consommateur peut également être exposé à la NDMA contenue dans d'autres produits tels que les cosmétiques et les produits de soins, les objets en caoutchouc et le tabac.

La NDMA est indubitablement cancérigène, comme le montrent les recherches en laboratoire selon lesquelles ce composé provoque l'apparition de tumeurs à dose relativement faible chez toutes les espèces étudiées. On a en outre la preuve indiscutable du

¹ Les nouvelles données notées par les auteurs et obtenues par un dépouillement de la littérature effectué avant la réunion du Comité d'évaluation finale ont été examinées compte tenu de leur influence probable sur les conclusions essentielles de la présente évaluation, le but étant avant tout d'établir si leur prise en compte serait prioritaire lors d'une prochaine mise à jour. Les auteurs ayant estimé qu'elles apportaient des éléments d'information supplémentaires, on a ajouté des données plus récentes encore que non essentielles pour la caractérisation des dangers ou l'analyse des relations dose-réponse.

pouvoir mutagène et clastogène de la NDMA. Le mécanisme de la cancérisation induite par ce composé n'est pas encore totalement élucidé, mais on sait qu'au cours de sa métabolisation, il donne naissance à un ion méthyldiazonium dont les adduits avec l'ADN (notamment l'*O*⁶-méthylguanine) jouent sans doute un rôle déterminant. Qualitativement, le métabolisme de la NDMA est analogue chez l'Homme et l'animal; on estime par conséquent que ce composé est très probablement également cancérigène pour l'Homme, sans doute à concentration relativement faible.

Comme on s'est surtout intéressé au pouvoir cancérigène de la NDMA, on ne dispose que de résultats de laboratoire limités concernant ses effets non néoplasiques. L'administration de doses répétées provoque des effets sur le foie et le rein et des études sur le développement consistant à administrer une dose unique ont mis en évidence une toxicité pour l'embryon pouvant aller jusqu'à la mort. Par ailleurs, on a fait état de divers effets immunologiques (dépression de l'immunité humorale et de l'immunité à médiation cellulaire) qui sont réversibles à faible concentration.

Il est clair que, s'agissant de la quantification de la relation dose-réponse en vue de la caractérisation du risque, c'est le cancer qui constitue le point d'aboutissement essentiel de l'action toxique de la NDMA. Outre que ce sont les effets les mieux caractérisés, en règle générale, ces tumeurs apparaissent à des concentrations beaucoup plus faibles que celles auxquelles des effets non néoplasiques sont habituellement observés. La dose tumorigène la plus faible ($CT_{0.5}$) pour l'apparition de tumeurs hépatiques (cystadénomes biliaires chez des rats femelles après exposition d'animaux des deux sexes) déterminée lors de l'étude qui a fourni les données essentielles sur ce point, a été de $34 \mu\text{g/kg}$ de poids corporel par jour. Cette valeur correspond à un risque unitaire de $1,5 \times 10^{-3}$ par μg de substance et par kg de poids corporel. En se basant sur l'estimation de la dose de NDMA absorbée avec l'air ambiant et une eau de boisson contaminée (eau souterraine) lors de la caractérisation du risque type, le risque au voisinage de sources industrielles ponctuelles de NDMA est évalué à $>10^{-5}$. En ce qui concerne le risque inhérent à la consommation d'eau de boisson contaminée, la valeur se situe entre 10^{-7} et 10^{-5} . La NDMA est un cancérigène génotoxique et l'exposition à ce composé doit être la plus faible possible.

On possède des données sur la toxicité aiguë et chronique du composé pour les organismes aquatiques. L'effet toxique constaté à la concentration la plus faible ($4000 \mu\text{g/litre}$) a consisté en une réduction de la croissance chez des algues. Cette caractérisation du risque type tient compte du fait que dans le pays retenu, la concentration en NDMA dans les eaux de surface est

inférieure au seuil estimatif d'apparition d'effets nocifs chez les organismes aquatiques. On n'a pas trouvé de données concernant la présence de NDMA dans les sédiments ou le sol du pays témoin.

RESUMEN DE ORIENTACIÓN

Este CICAD sobre la *N*-nitrosodimetilamina (NDMA), preparado conjuntamente por la Dirección de Higiene del Medio del Ministerio de Salud del Canadá y la División de Evaluación de Productos Químicos Comerciales del Ministerio de Medio Ambiente del Canadá, se basa en la documentación preparada al mismo tiempo como parte del Programa de Sustancias Prioritarias en el marco de la *Ley Canadiense de Protección del Medio Ambiente* (CEPA). Las evaluaciones de sustancias prioritarias previstas en la CEPA tienen por objeto valorar los efectos potenciales para la salud humana de la exposición indirecta en el medio ambiente general, así como los efectos ecológicos. Aunque en el documento original no se abordó la exposición ocupacional (Ministerios de Medio Ambiente y de Salud del Canadá, 2001), en el presente CICAD se ha incluido información sobre este aspecto. En este examen se analizaron los datos identificados hasta el final de agosto de 1998 (efectos medioambientales) y agosto de 1999¹ (efectos en la salud humana). También se consultaron otros exámenes, entre ellos los del CIIC (1978), ATSDR (1989), OME (1991, 1998) y BIBRA Toxicology International (1997, 1998). La información relativa al carácter del examen colegiado y la disponibilidad del documento original figuran en el apéndice 1. La información sobre el examen colegiado de este CICAD aparece en el apéndice 2. Este CICAD se aprobó como evaluación internacional en una reunión de la Junta de Evaluación Final celebrada en Ginebra (Suiza) del 8 al 12 de enero de 2001. La lista de participantes en esta reunión figura en el apéndice 3. La Ficha internacional de seguridad química (ICSC 0525) para la NDMA, preparada por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1993), también se reproduce en este documento.

La *N*-nitrosodimetilamina (NDMA) es la dialquil-nitrosamina más sencilla. Aunque ya no se utiliza con fines industriales o comerciales en el Canadá o los Estados Unidos de América, se sigue liberando como subproducto y contaminante a partir de diversas

industrias y de instalaciones de depuración de aguas residuales municipales. Las emisiones más importantes de NDMA proceden de la fabricación de plaguicidas, neumáticos de caucho, alquilaminas y colorantes. La NDMA se puede formar también en condiciones naturales en el aire, el agua y el suelo como resultado de procesos químicos, fotoquímicos y biológicos, y se ha detectado en el agua de bebida y en los gases de escape de los automóviles.

La fotólisis es la vía principal de eliminación de la NDMA de las aguas superficiales, el aire y el suelo. Sin embargo, en las aguas superficiales con concentraciones elevadas de sustancias orgánicas y materia en suspensión, la fotodegradación es mucho más lenta. En las aguas no superficiales y en el suelo, la biodegradación es la vía de eliminación más importante. Es poco probable que la NDMA recorra largas distancias suspendida en el aire o que se distribuya en el suelo y los sedimentos. Debido a su solubilidad y a su bajo coeficiente de reparto, la NDMA puede filtrarse a las aguas freáticas y persistir en ellas. Se metaboliza y no se bioacumula. En general, la NDMA no es detectable en las aguas superficiales, excepto en la contaminación localizada de zonas industriales, en las que se han medido concentraciones de efluentes de la etapa final de producción de hasta 0,266 µg/l.

En estudios limitados en el país en el cual se basa la caracterización del riesgo de muestra (es decir, el Canadá), no se ha detectado NDMA en el aire, salvo en las inmediaciones de zonas industriales. Se han detectado concentraciones bajas de NDMA en el agua de bebida, por ejemplo en instalaciones de tratamiento del agua o a partir de aguas freáticas contaminadas por efluentes industriales. Se ha demostrado la presencia de NDMA en algunos alimentos, en particular la cerveza, la carne curada, los productos pesqueros y algunos quesos, aunque en los últimos años las concentraciones de NDMA en estos productos han disminuido debido a cambios en la elaboración de los alimentos. También se puede sufrir exposición a la NDMA por el uso de productos de consumo que la contienen, por ejemplo cosméticos y productos de cuidado personal, productos que contienen caucho y productos de tabaco.

Sobre la base de los estudios de laboratorio en los cuales se han inducido tumores en todas las especies examinadas a dosis relativamente bajas, la NDMA es claramente carcinogénica. Hay pruebas abundantes de que la NDMA es mutagénica y clastogénica. Aunque no se conoce completamente su mecanismo de inducción de tumores, los aductos de ADN (en particular la *O*⁶-metilguanina) formados por el ión metildiazonio generado durante el metabolismo tienen probablemente un papel decisivo. Desde el punto de vista cualitativo, el metabolismo de la NDMA parece ser semejante en las personas

¹ Se ha incluido nueva información destacada por los examinadores y obtenida en una búsqueda bibliográfica realizada antes de la reunión de la Junta de Evaluación Final para señalar sus probables repercusiones en las conclusiones esenciales de esta evaluación, principalmente con objeto de establecer la prioridad para su examen en una actualización. Se ha añadido información más reciente, no esencial para la caracterización del peligro o el análisis de la exposición-respuesta, que a juicio de los examinadores aumentaba el valor informativo.

y los animales; en consecuencia, se considera muy probable que sea carcinogénica para las personas, incluso a niveles de exposición relativamente bajos.

Los datos sobre los efectos no neoplásicos en animales de laboratorio asociados con la exposición a la NDMA son limitados y pueden atribuirse principalmente a la atención que se presta a su carcinogenicidad. Se han notificado efectos en el hígado y el riñón en estudios de toxicidad de dosis repetidas, toxicidad y letalidad embrionarias en estudios de desarrollo de dosis única y una serie de efectos inmunológicos (supresión de la inmunidad humoral y mediada por células) reversibles con las concentraciones más bajas.

El cáncer es sin duda el efecto final crítico para la cuantificación de la exposición-respuesta en la caracterización del riesgo de la NDMA. Además de ser el mejor caracterizado, en general, los tumores se producen con la concentración más baja, en comparación con las notificadas normalmente como inductoras de efectos distintos del cáncer. La dosis tumorigénica_{0.5} más baja para la inducción de tumores hepáticos en ratas macho y hembra expuestas a la NDMA en el estudio crítico fue de 34 µg/kg de peso corporal al día para la formación de cistadenomas biliares en hembras. Esto equivale a un riesgo unitario de $1,5 \times 10^{-3}$ por µg/kg de peso corporal. Basándose en la ingesta estimada de NDMA en el aire y en el agua de bebida contaminada (agua freática) en la caracterización del riesgo de muestra, los riesgos en las inmediaciones de fuentes puntuales industriales son $>10^{-5}$. Los relativos al agua de bebida son de 10^{-7} a 10^{-5} . La NDMA es un carcinógeno genotóxico y la exposición se debe reducir en la medida de lo posible.

Hay datos disponibles de toxicidad aguda y crónica para los organismos acuáticos. El efecto tóxico que se produjo con la concentración más baja fue una reducción del crecimiento de las algas con 4000 µg/l. En la caracterización del riesgo de muestra, las concentraciones de NDMA en las aguas superficiales del país en el que se ha realizado es inferior al umbral para los efectos adversos estimados en los organismos acuáticos. No se encontraron datos sobre las concentraciones de la NDMA en los sedimentos o en el suelo del país de muestra.

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Exhibit L



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FAST TRACK

Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study

Anton Pottegård,¹ Kasper Bruun Kristensen,¹ Martin Thomsen Ernst,¹ Nanna Borup Johansen,² Pierre Quartarolo,³ Jesper Hallas¹

¹Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, JB Winsløvsvej 19, 2, 5000 Odense C, Denmark

²Medical Evaluation and Biostatistics, Danish Medicines Agency, Copenhagen, Denmark

³Pharmacovigilance and Medical Devices, Danish Medicines Agency, Copenhagen, Denmark

Correspondence to: A Pottegård
apottegaard@health.sdu.dk

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Cite this as: *BMJ* 2018;362:k3851
<http://dx.doi.org/10.1136/bmj.k3851>

Accepted: 09 September 2018

ABSTRACT**OBJECTIVE**

To perform an expedited assessment of cancer risk associated with exposure to N-nitrosodimethylamine (NDMA) through contaminated valsartan products.

DESIGN

Nationwide cohort study.

SETTING

Danish health registries on individual level prescription drug use, cancer occurrence, and hospital diagnoses.

PARTICIPANTS

5150 Danish patients with no history of cancer, aged 40 years or older, and using valsartan at 1 January 2012 or initiating use between 1 January 2012 and 30 June 2017. Participants were followed from one year after cohort entry (lag time period) until experiencing a cancer outcome, death, migration, or end of study period (30 June 2018). Each participant's exposure to NDMA (ever exposure and predefined categories of cumulative valsartan exposure) was mapped out as a time varying variable while also applying a one year lag.

MAIN OUTCOME MEASURES

Association between NDMA exposure and a primary composite endpoint comprising all cancers except non-melanoma skin cancer, estimated using Cox regression. In supplementary analyses, the risk of individual cancers was determined.

RESULTS

The final cohort comprised 5150 people followed for a median of 4.6 years. In total, 3625 cohort participants contributed 7344 person years classified as unexposed to NDMA, and 3450 participants contributed 11920 person years classified as ever exposed to NDMA. With 104 cancer outcomes among NDMA unexposed participants and 198 among exposed participants, the adjusted hazard ratio for overall cancer was 1.09 (95% confidence interval 0.85 to 1.41), with no evidence

of a dose-response relation ($P=0.70$). For single cancer outcomes, increases in risk were observed for colorectal cancer (hazard ratio 1.46, 95% confidence interval 0.79 to 2.73) and for uterine cancer (1.81, 0.55 to 5.90), although with wide confidence intervals that included the null.

CONCLUSIONS

The results do not imply a markedly increased short term overall risk of cancer in users of valsartan contaminated with NDMA. However, uncertainty persists about single cancer outcomes, and studies with longer follow-up are needed to assess long term cancer risk.

Introduction

Valsartan is an angiotensin II receptor antagonist used to treat hypertension and heart failure.^{1 2} In July 2018, some valsartan products were discovered to have been contaminated with N-nitrosodimethylamine (NDMA).³ This contamination, which far exceeded regulatory exposure limits, was specific to drug products manufactured by Zhejiang Huahai Pharmaceuticals, a company in Linhai, China, and seems to be related to a change in the manufacturing process that was implemented in 2012. Consequently, medical agencies across Europe as well as the US Food and Drug Administration have withdrawn all affected valsartan products from the market as of July 2018.³

NDMA is the simplest dialkyl nitrosamine and is known to be a by-product in various industries—for example, the manufacture of pesticides, rubber tyres, alkylamines, and dyes.⁴ NDMA is one of the most well characterised and most potent animal carcinogens known and has been shown to be a potent carcinogen across all species that have been investigated, both as single doses and with long term exposure to lower quantities.⁵ Although no in vivo data are available for humans, NDMA seems to be metabolised similarly in human tissue and rodent tissue.⁶ The International Agency for Research on Cancer (IARC) has on this basis classified NDMA as “probably carcinogenic to humans” (group 2A), emphasising that NDMA “should be regarded for practical purposes as if it were carcinogenic to humans.”⁷

We accessed the nationwide Danish healthcare registries and conducted an expedited observational cohort study of the association between use of potentially NDMA contaminated valsartan products and risk of cancer. Our aim was to quantify the potential consequences of NDMA contaminated drug products entering the market and to provide timely information for regulatory bodies evaluating this potential public health issue.

EXHIBIT

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Some valsartan products are suspected of having been contaminated with N-nitrosodimethylamine (NDMA), which is classified as carcinogenic to humans. After the discovery, European medical agencies and the US Food and Drug Administration withdrew affected valsartan products from the market.

WHAT THIS STUDY ADDS

Among Danish valsartan users, exposure to NDMA contaminated valsartan was not associated with a markedly increased risk of overall cancer (adjusted hazard ratio 1.09, 95% confidence interval 0.85 to 1.41).

Future studies are, however, required to evaluate the risks for single cancer outcomes as well as long term effects.

Methods

We conducted a cohort study comparing cancer outcomes in users of potentially NDMA contaminated valsartan products with users of valsartan products assumed free from this contaminant.

Data sources and linkage

We obtained data from four Danish nationwide registries: the Danish Cancer Registry,^{8,9} the National Prescription Registry,¹⁰ the National Patient Register,¹¹ and the Civil Registration System.¹² Supplementary appendix A describes the data sources in detail and appendix B provides the codes for cancer diagnoses, drug exposures, and covariates. Data were linked by the personal identification number, a unique identifier assigned to all Danish residents since 1968.¹³ Virtually all medical care in Denmark is provided by the national health authorities, allowing population based register linkage studies covering all legal residents of Denmark.

Study cohort

The study cohort comprised all Danish patients filling a valsartan prescription during the study period of 1 January 2012 to 30 June 2018. Prevalent users of valsartan at the start of the study period—defined as individuals having filled a valsartan prescription in September to the end of December 2011, entered the study cohort at 1 January 2012, whereas incident users entered the study cohort at the day of filling their first valsartan prescription during the study period. As patients contributed risk time from one year after entering the study cohort, we excluded those with less than one year of follow-up, as they did not contribute to any of the analyses reported. For the same reason, we excluded incident users filling their first prescription after 30 June 2017. We further excluded patients with a record of a previous cancer except non-melanoma skin cancer; those with a recent migration before cohort entry (within two years) to ensure enough baseline data on all study participants; and those aged less than 40 years at cohort entry as both use of valsartan and cancer occurrence is rare among children and younger adults. Participants were followed until a cancer outcome, death, migration, or end of the study period (30 June 2018), whichever occurred first.

Ascertainment of NDMA exposure

Within the study cohort we mapped out each participant's exposure to NDMA contamination using the unique drug ID (Nordic article number) as recorded in the National Prescription Registry to identify the single valsartan product and its manufacturer. From the 128 unique valsartan drug products used during 2012-18 within our study population, we identified 18 drug products (which constituted 18% of all prescriptions filled) that were manufactured using an active pharmaceutical ingredient from Zhejiang Huahai Pharmaceuticals. These drug products were classified as probably contaminated with NDMA. An additional 36 drug products (26% of all prescriptions) were classified as possibly contaminated with NDMA,

as they contained an active pharmaceutical ingredient both from Zhejiang Huahai Pharmaceuticals and from other companies. Seventy four drug products (55% of all prescriptions) were classified as unlikely to be contaminated with NDMA as they did not contain an active pharmaceutical ingredient from Zhejiang Huahai Pharmaceuticals. In the main analysis we pooled together valsartan prescriptions classified as probably and possibly contaminated with NDMA, classifying those filling such prescriptions as ever exposed to NDMA from their first occurrence of such a prescription. We further stratified NDMA exposed person time by cumulative dose from filled prescriptions of potentially NDMA containing valsartan tablets (applying preplanned strata of <20 000, 20 000-49 999, and ≥50 000 mg). The use of milligrams of valsartan as a scale for the dose-response analysis was based on the observation that the NDMA content for each tablet seems to correlate with the strength of the tablet.¹⁴ With an estimated daily use of 80-160 mg (the defined daily dose of valsartan is 80 mg¹⁵), these cut-offs corresponded roughly to <200, 200-499, and ≥500 tablets. Of note, individuals classified as exposed to NDMA contributed follow-up to the non-exposed cohort until filling their first prescription for a potentially NDMA contaminated product. This ensured that the estimates were not affected by immortal time bias.¹⁶

Throughout all assessments of potential exposure to NDMA, we applied a one year lag time—that is, persons contributed NDMA exposed person time from one year after having filled their first prescription for a potentially NDMA containing valsartan product and onwards. This was done as very recent NDMA exposure (<1 year) is considered unlikely to materially affect an individual's risk of receiving a cancer diagnosis.¹⁷ The length of the lag time was subjected to sensitivity analyses.

Cancer outcomes

We obtained cancer outcomes from the Danish Cancer Registry.^{8,9} However, as data in this registry is currently only updated to 2016, we used the Danish National Patient Registry¹¹ to ascertain outcomes from 1 January 2017 to 30 June 2018. The primary outcome was a composite endpoint comprising all cancers (except non-melanoma skin cancer), as NDMA exposure is suspected to increase the risk of several different cancers. In supplementary analyses, we determined the risk of individual cancers, grouping cancers by organ system (ie, using codes from the international classification of diseases, 10th revision).

Covariates

The study cohort was described according to several characteristics that were also incorporated as covariates in the analyses: use of drugs (prescription fill <120 days before cohort entry) known or suspected to affect cancer risk, including low dose aspirin, non-aspirin non-steroidal anti-inflammatory drugs, 5-α reductase inhibitors, statins, spironolactone, oral

steroids, hormone replacement therapy, and selective serotonin reuptake inhibitors¹⁸; prior diagnoses (within five years from cohort entry) of diabetes, chronic obstructive pulmonary disease, heart failure, and alcohol related disease; Charlson comorbidity index scores (0, low; 1-2, medium; or ≥ 3 , high; based on diagnoses established within the past five years before cohort entry)^{19 20}; and whether the participant was a prevalent valsartan user at the beginning of the study period or initiated valsartan during the study period.

Main analysis

The primary analysis comprised a comparison of cancer occurrence during follow-up exposed to NDMA versus follow-up not exposed to NDMA. We used Cox regression to estimate the hazard ratio with 95% confidence intervals for cancer associated with NDMA exposure, both for ever use and for the predefined categories of cumulative use. The proportional hazards assumption was tested using Schoenfeld residuals. We carried out a formal dose-response test by categorising cumulative exposure to NDMA contaminated valsartan in categories of 10 000 mg as a time varying exposure and obtaining the P value for this variable as a continuous predictor of cancer risk in a Cox regression. As all comparisons were performed within users of valsartan, the exposure to NDMA can reasonably be expected to be a random event, and confounding is thus expected to be limited. Analyses were, however, performed as crude comparisons adjusted only for sex and age (age at cohort entry as continuous variable) as well as adjusted for sex, age, and the potential confounding factors. All analyses were performed using STATA Release 15.2.

Sensitivity and supplementary analyses

We carried out several sensitivity and supplementary analyses. Firstly, we performed analyses stratifying all participants by sex and age (40-69 and ≥ 70 years at cohort entry). Secondly, we restricted the cohort to prevalent valsartan users at the start of the study and to incident users during the study period. Thirdly, we restricted the ascertainment of NDMA exposure to prescriptions classified as probably contaminated with NDMA, while censoring individuals filling a prescription for a possibly NDMA contaminated drug product from the reference cohort (although allowing them to later enter the NDMA exposed cohort). Lastly, we varied the one year lag time period applied in the main analysis to six months and two years.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing of results. There are no plans to disseminate the results of the research directly to the patient community. However, the results will be included in the ongoing review of the potential

impact of NDMA contaminated valsartan on patients by the European Medicines Agency.

Results

In initial descriptive analyses, we identified 7068 unique individuals filling a total of 95 650 valsartan prescriptions from January 2012 to June 2018, the period where NDMA contaminated products were on the Danish market. The overall use of valsartan increased slightly during this period, in particular in 2017 and 2018 (fig 1), and the use of valsartan products possibly or probably contaminated with NDMA constituted about half of the total valsartan use, although this proportion dropped slightly during 2017-18.

For the selection of the study cohort, we identified 6406 individuals filling a valsartan prescription between September 2011 and June 2017. Of these, 5150 unique individuals met our inclusion criteria and entered the final cohort (fig 2), contributing a median of 4.6 years (interquartile range 2.0-5.5 years) of follow-up to the analysis, after the application of a one year lag period. Table 1 includes the baseline characteristics of valsartan users entering the study. A total of 3625 participants contributed 7344 person years of follow-up classified as unexposed to NDMA, and 3450 participants contributed 11 920 person years classified as ever exposed to NDMA (fig 2). The distribution of potentially NDMA contaminated and non-contaminated prescriptions were similar between the study cohort and all valsartan users (see supplementary figure 1).

Overall, exposure to potentially (probably or possibly) NDMA contaminated valsartan products showed no association with cancer compared with exposure to valsartan products unlikely to be contaminated with NDMA (adjusted hazard ratio 1.09, 95% confidence interval 0.85 to 1.41) and no evidence of a dose-response relation ($P=0.70$, table 2).

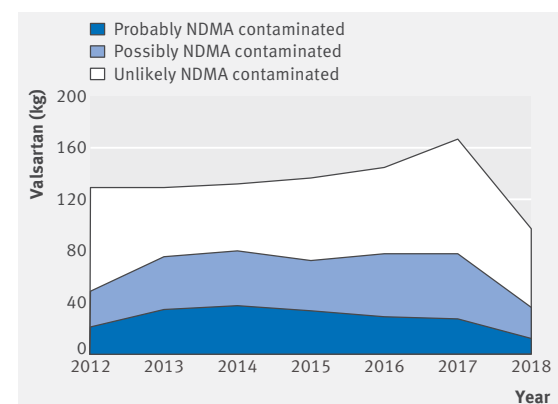


Fig 1 | Use of valsartan in kilograms of active substance, specified by drug products classified as probably, possibly, or unlikely to be contaminated with N-nitrosodimethylamine (NDMA). The drop in 2018 results from data only being available to June 2018

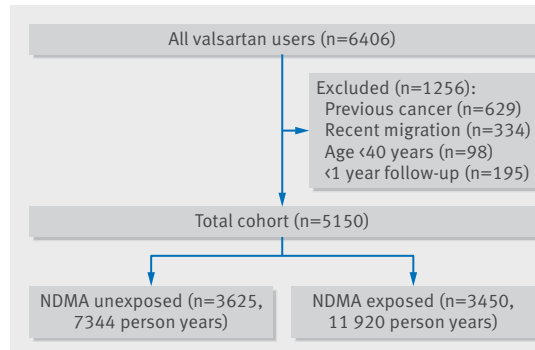


Fig 2 | Flowchart of cohort selection of Danish users of valsartan, January 2012 to June 2018. NDMA=N-nitrosodimethylamine

In analyses of single cancer outcomes, increased risks were seen for colorectal cancer (hazard ratio 1.46, 95% confidence interval 0.79 to 2.73) and for uterine cancer (1.81, 0.55 to 5.90), although neither these nor other single cancer outcomes reached statistical significance (fig 3). Analyses of other cancer outcomes were not possible owing to low numbers—that is, no cancer outcomes outside those included in figure 3 showed any associations with NDMA use.

Results comparable to the main analyses were found when we stratified by sex and age, whereas a

stronger association was seen when we restricted to incident users during the study period (hazard ratio 1.58, 95% confidence interval 0.99 to 2.52) compared with prevalent users at the beginning of the study period (0.91, 0.66 to 1.25) (fig 4). A test for interaction between being an incident valsartan user and the effect of exposure to NDMA yielded a p value of 0.059.

The sensitivity analysis censoring individuals filling a prescription for a possibly NDMA contaminated valsartan product from the reference category yielded results comparable to those of the main analyses, both for overall cancer (see supplementary table 1) and for single cancers (see supplementary figure 2).

Varying the lag time from one year used in the main analyses to six months or two years yielded slightly higher risk estimates with increasing lag time, with the hazard ratio for ever exposure increasing to 1.17 (95% confidence interval 0.88 to 1.55) when a two year lag time was applied, although this did not reach statistical significance (see supplementary table 2).

Discussion

In this nationwide cohort study of Danish valsartan users, we did not see an increased short term overall risk of cancer associated with the use of valsartan products potentially contaminated with N-nitrosodimethylamine (NDMA).

Table 1 | Baseline characteristics of valsartan users entering study and among those potentially exposed and not exposed to N-nitrosodimethylamine (NDMA)

Characteristics	All (n=5150)	NDMA exposure	
		Exposed* (n=3450)	Not exposed* (n=3625)
Sex:			
Men	2531 (49.1)	1630 (46.9)	1745 (43.6)
Women	2619 (50.9)	1820 (53.1)	1880 (56.4)
Age (years):			
Median (interquartile range)	66 (58-74)	-	-
40-69	3195 (62.0)	2197 (65.0)	2164 (61.2)
≥70	1955 (38.0)	1253 (35.0)	1461 (38.8)
Prevalent valsartan users†:			
No	2870 (55.7)	2012 (51.2)	1353 (25.7)
Yes	2280 (44.3)	1438 (48.8)	2272 (74.3)
Charlson comorbidity score:			
0 (low)	3864 (75.0)	2697 (79.0)	2635 (74.9)
1	884 (17.2)	541 (15.3)	670 (17.1)
2	217 (4.2)	117 (3.2)	168 (4.5)
≥3 (high)	185 (3.6)	95 (2.5)	152 (3.4)
Drugs:			
Low dose aspirin	1388 (27.0)	842 (25.2)	1092 (29.2)
Non-aspirin NSAID	772 (15.0)	533 (15.5)	513 (16.0)
Statins	1924 (37.4)	1185 (35.1)	1457 (37.4)
Spironolactone	405 (7.9)	117 (3.2)	362 (4.9)
Glucocorticoids for systemic use	244 (4.7)	166 (4.5)	171 (4.3)
5-α reductase inhibitors	64 (1.2)	41 (1.2)	47 (0.9)
SSRIs	299 (5.8)	196 (5.7)	223 (6.0)
Hormone replacement therapy	454 (8.8)	319 (9.8)	338 (9.9)
Diagnoses:			
Diabetes type 1 and 2	899 (17.5)	559 (16.1)	667 (18.0)
Chronic obstructive pulmonary disease	247 (4.8)	131 (3.5)	200 (4.3)
Congestive heart failure	535 (10.4)	117 (2.9)	497 (5.3)
Alcohol related disease	48 (0.9)	28 (0.7)	34 (0.7)

NSAID=non-steroidal anti-inflammatory drug; SSRIs=selective serotonin reuptake inhibitors.

*Characteristics weighted by proportion of total time exposed or not exposed that individuals contributed, thereby providing the distribution of covariates in the main analysis comparison.

†Defined as being included in the study at 1 January 2012 by having filled a valsartan prescription between September and December 2011.

Table 2 | Estimates for association between use of valsartan products potentially contaminated with N-nitrosodimethylamine (NDMA) and cancer risk compared with non-contaminated valsartan products

NDMA exposure	Follow-up (person years)	Cancer outcomes	Incidence rate (/1000 person years)	Adjusted hazard ratio* (95% CI)	Fully adjusted hazard ratio† (95% CI)
Never use	7344	104	14.2	1.00 (ref)	1.00 (ref)
Ever exposure	11 920	198	16.6	1.16 (0.91 to 1.49)	1.09 (0.85 to 1.41)
Cumulative exposure (mg)‡:					
<20 000	3776	67	17.7	1.26 (0.92 to 1.72)	1.15 (0.83 to 1.59)
20000-49 999	2836	44	15.5	1.07 (0.75 to 1.53)	0.99 (0.69 to 1.43)
≥50 000	5308	87	16.4	1.14 (0.84 to 1.54)	1.11 (0.82 to 1.50)
Test for trend§				P=0.65	P=0.70

*Adjusted for age and sex.

†Adjusted for sex, age, use of low dose aspirin, non-aspirin non-steroidal anti-inflammatory drugs, 5- α reductase inhibitors, statins, spironolactone, oral steroids, hormone replacement therapy, or selective serotonin reuptake inhibitors, history of diabetes, chronic obstructive pulmonary disease, heart failure, or alcohol related disease, Charlson comorbidity index score, and being a prevalent valsartan user.

‡Defined by total amount of NDMA contaminated valsartan filled.

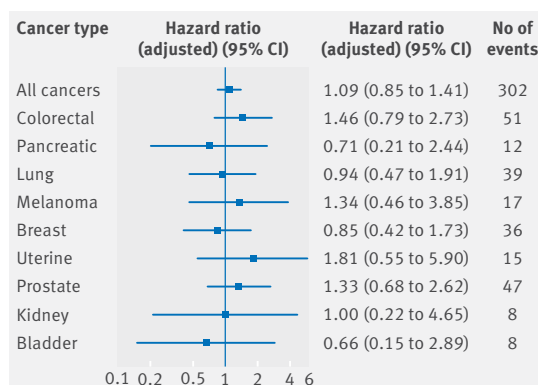
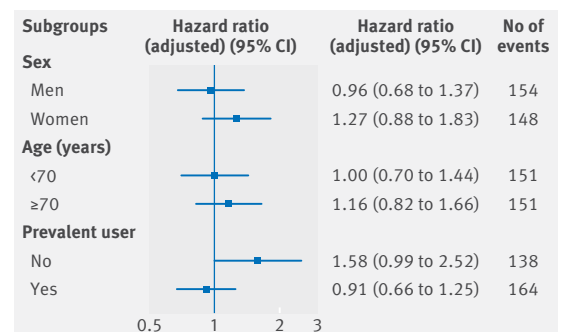
§Estimated using Cox regression across 10 000 mg strata of NDMA contaminated valsartan filled.

Strengths and limitations of this study

The principal strength of this study is the use of high quality nationwide registries,^{9 10 11} leaving little potential for selection bias.¹² Furthermore, the use of dispensing data, instead of data on prescribed drugs, as a proxy for NDMA exposure reduces the risk of misclassification due to primary non-adherence.²¹ The principal weakness of the study is the limited median follow-up. Our findings only pertain to early cancer risk after exposure to NDMA whereas future studies are needed to elucidate the total cancer risk, which requires a substantially longer follow-up for the individual than what is currently available. Additionally, the limited follow-up combined with the low use of valsartan in Denmark leads to limited precision. Lastly, our exposure ascertainment is based on assumptions about NDMA content. Reassuringly, our sensitivity analysis disregarding less certain sources of NDMA returned estimates comparable to those of the main analysis. However, future studies should utilise data on the actual NDMA content of individual valsartan tablets once such information becomes available.

Biological rationale

The International Agency for Research on Cancer (IARC) has classified NDMA as “probably carcinogenic to humans” owing to limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animal studies.⁷ NDMA is suspected to have both localised and systemic carcinogenic effects due to the induction of DNA-damaging metabolites in the gastrointestinal tract and liver.^{6 22} Specifically, in the liver, NDMA is metabolised by CYP2E1 to methyldiazonium, which causes mutations by methylation.²³ Also, N-nitroso compounds such as NDMA activate *ras* oncogenes, which are thought to play a role in the development of colon cancer.⁶ As such, tumours in the gastrointestinal tract, lungs, kidneys, and liver have been seen in animal studies.^{5 23 24} Evidence of carcinogenicity in rats was found at doses of about 10 $\mu\text{g/kg/day}$.²³ With concentrations of up to 22 μg NDMA in 320 mg valsartan tablets and 10 μg NDMA in 160 mg tablets,¹⁴ the daily exposure for a 70 kg person ranges from 0.14 to 0.31 $\mu\text{g/kg/day}$. Even though it is not possible to extrapolate directly from animals to humans, the daily exposure in humans is thus roughly 30 times lower than the lowest dose leading to liver cancer in rats. Owing to the known carcinogenic effect of NDMA in animals,

**Fig 3 | Estimates for association between use of potentially N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of single cancer outcomes compared with users of non-contaminated valsartan products. Number of events are total number of events among valsartan users****Fig 4 | Estimates for association between use of potentially N-nitrosodimethylamine (NDMA) contaminated valsartan products and cancer risk compared with users of non-contaminated valsartan products, specified by patient subgroups. Number of events are total number of events among valsartan users**

no experimental studies in humans exist. However, as some dietary products (eg, processed meat) are known to contain small amounts of NDMA, epidemiological studies based on food frequency questionnaire data have been performed. Even though such studies are highly prone to confounding, three found an increased risk of gastrointestinal cancer with exposure to NDMA, predominantly colorectal cancer.^{25 26 27} This finding, together with that from the animal studies, provides some support for the increased although statistically non-significant risk for this particular cancer observed in our study. Only one previous paper has reported on uterine cancer, finding no association between exposure to NDMA and uterine cancer in rats.²⁸ Lastly, no estimates could be obtained for liver cancer in our study owing to the absence of liver cancer events among those exposed to NDMA. A markedly increased risk of liver cancer associated with NDMA exposure thus seems unlikely.

Principal findings

Our estimates pertain to early cancer risk associated with exposure to NDMA through contaminated valsartan products and should not be interpreted as evidence against NDMA being carcinogenic to humans in general. At most, our findings suggest that the levels of NDMA exposure achieved through valsartan products do not translate into a substantially increased short term cancer risk. Furthermore, the fact that our study evaluates a potential safety concern holds some implications about how to interpret the results. While the estimate for our primary outcome suggests a negligible and statistically non-significant increase in cancer risk of 9%, it might be argued that a more cautious interpretation, reflecting the nature of the study question, would be to consider the upper limit of the confidence interval. Doing so leads to the different, although related, conclusion that we can reasonably exclude a more than 40% increased short term risk of cancer from exposure to NDMA contaminated valsartan products. A similar interpretation of the estimates obtained for the single cancer outcomes—in particular colorectal and uterine cancer—clearly highlights that our study cannot confidently rule out an increased risk from exposure to NDMA.

The finding that exposure to NDMA was associated with an increased risk of cancer specifically among users initiating valsartan treatment during the study period, as opposed to among valsartan users prevalent at the beginning of the study period, was a surprising finding that we cannot explain. The duration of follow-up was on average longer for prevalent users, as they were followed from the beginning of the study period (1 January 2012), and a late effect of exposure to NDMA therefore cannot explain this finding, as it would have led to an increased risk specifically among prevalent and not incident valsartan users. Considering the uncertainty about the actual NDMA content of valsartan products, it could be speculated that those using valsartan later in the study period might have been exposed to NDMA more often. However, no data

are available that can be used to test this hypothesis. Lastly, our subgroup analyses had limited power and therefore the possibility of our results being a chance finding should also be considered.

Policy implications

Our findings can support regulators in their evaluation of the potential public health impact of exposure to NDMA through valsartan products. The Danish nationwide health registries and the strong research infrastructure hosted by Statistics Denmark and the Danish Health Data Authority, the latter of which was used in this study, gives researchers and regulators a unique possibility to provide answers to such emerging public health concerns in a timely manner. The present analysis was completed and submitted for publication within seven weeks after the finding of NDMA in valsartan products was announced publicly, and the paper published in *The BMJ* after a fast track peer review process spanning only three weeks from submission to publication. We previously performed a similar expedited assessment of a putative bleeding risk associated with use of generic warfarin,^{29 30} although its publication was delayed by the peer review process for several months. Besides rapid peer review assessment, a close collaboration between researchers and regulators is a key element in ensuring both speed and relevance of such research projects. In addition to knowledge about the risks associated with exposure to NDMA, the present study provides proof-of-concept for such processes, which hold great promise for the use of pharmacoepidemiological input in the regulatory assessment of future public health crises.

Conclusion

We have assessed the potential cancer risk associated with exposure to NDMA through contaminated valsartan products and found no evidence of a markedly increased short term overall risk of cancer. However, we cannot exclude a modest association. Furthermore, owing to the limited follow-up, assessment of long term effects was not possible, and the low number of events makes interpretation of estimates for single cancer outcomes difficult. Therefore, further studies are needed to fully elucidate the health effects of NDMA contaminated valsartan products.

We thank the Danish Health Data Authority, in particular Anna Birkmose Andersen and Anders Schierup, for providing expedited access to the registry data used in the study; Nicolai C Brun (Danish Medicines Agency) for valuable comments on the interpretation of the findings; and Camilla Ærtebjerg Bæk (Danish Medicines Agency) for providing toxicological input.

Contributors: AP, JH, PQ, and NBJ conceived and designed the study. AP, KBK, and MTE performed the statistical analyses and data management. AP and KBK drafted the initial manuscript. All authors interpreted the data and revised the manuscript critically. AP is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: None.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial

relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: Statistical code is available from AP upon request. No additional data are available as Danish legislation does not allow disclosure of individual level data.

Transparency: The lead author (AP) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Supplementary information: appendices A and B

Exhibit M



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FAST TRACK

Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study

Anton Pottegård,¹ Kasper Bruun Kristensen,¹ Martin Thomsen Ernst,¹ Nanna Borup Johansen,² Pierre Quartarolo,³ Jesper Hallas¹

¹Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, JB Winsløvsvej 19, 2, 5000 Odense C, Denmark

²Medical Evaluation and Biostatistics, Danish Medicines Agency, Copenhagen, Denmark

³Pharmacovigilance and Medical Devices, Danish Medicines Agency, Copenhagen, Denmark

Correspondence to: A Pottegård
apottegaard@health.sdu.dk

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2018;362:k3851
<http://dx.doi.org/10.1136/bmj.k3851>

Accepted: 09 September 2018

ABSTRACT

OBJECTIVE

To perform an expedited assessment of cancer risk associated with exposure to N-nitrosodimethylamine (NDMA) through contaminated valsartan products.

DESIGN

Nationwide cohort study.

SETTING

Danish health registries on individual level prescription drug use, cancer occurrence, and hospital diagnoses.

PARTICIPANTS

5150 Danish patients with no history of cancer, aged 40 years or older, and using valsartan at 1 January 2012 or initiating use between 1 January 2012 and 30 June 2017. Participants were followed from one year after cohort entry (lag time period) until experiencing a cancer outcome, death, migration, or end of study period (30 June 2018). Each participant's exposure to NDMA (ever exposure and predefined categories of cumulative valsartan exposure) was mapped out as a time varying variable while also applying a one year lag.

MAIN OUTCOME MEASURES

Association between NDMA exposure and a primary composite endpoint comprising all cancers except non-melanoma skin cancer, estimated using Cox regression. In supplementary analyses, the risk of individual cancers was determined.

RESULTS

The final cohort comprised 5150 people followed for a median of 4.6 years. In total, 3625 cohort participants contributed 7344 person years classified as unexposed to NDMA, and 3450 participants contributed 11920 person years classified as ever exposed to NDMA. With 104 cancer outcomes among NDMA unexposed participants and 198 among exposed participants, the adjusted hazard ratio for overall cancer was 1.09 (95% confidence interval 0.85 to 1.41), with no evidence

of a dose-response relation ($P=0.70$). For single cancer outcomes, increases in risk were observed for colorectal cancer (hazard ratio 1.46, 95% confidence interval 0.79 to 2.73) and for uterine cancer (1.81, 0.55 to 5.90), although with wide confidence intervals that included the null.

CONCLUSIONS

The results do not imply a markedly increased short term overall risk of cancer in users of valsartan contaminated with NDMA. However, uncertainty persists about single cancer outcomes, and studies with longer follow-up are needed to assess long term cancer risk.

Introduction

Valsartan is an angiotensin II receptor antagonist used to treat hypertension and heart failure.^{1 2} In July 2018, some valsartan products were discovered to have been contaminated with N-nitrosodimethylamine (NDMA).³ This contamination, which far exceeded regulatory exposure limits, was specific to drug products manufactured by Zhejiang Huahai Pharmaceuticals, a company in Linhai, China, and seems to be related to a change in the manufacturing process that was implemented in 2012. Consequently, medical agencies across Europe as well as the US Food and Drug Administration have withdrawn all affected valsartan products from the market as of July 2018.³

NDMA is the simplest dialkyl nitrosamine and is known to be a by-product in various industries—for example, the manufacture of pesticides, rubber tyres, alkylamines, and dyes.⁴ NDMA is one of the most well characterised and most potent animal carcinogens known and has been shown to be a potent carcinogen across all species that have been investigated, both as single doses and with long term exposure to lower quantities.⁵ Although no in vivo data are available for humans, NDMA seems to be metabolised similarly in human tissue and rodent tissue.⁶ The International Agency for Research on Cancer (IARC) has on this basis classified NDMA as “probably carcinogenic to humans” (group 2A), emphasising that NDMA “should be regarded for practical purposes as if it were carcinogenic to humans.”⁷

We accessed the nationwide Danish healthcare registries and conducted an expedited observational cohort study of the association between use of potentially NDMA contaminated valsartan products and risk of cancer. Our aim was to quantify the potential consequences of NDMA contaminated drug products entering the market and to provide timely information for regulatory bodies evaluating this potential public health issue.

EXHIBIT

13

WHAT IS ALREADY KNOWN ON THIS TOPIC

Some valsartan products are suspected of having been contaminated with N-nitrosodimethylamine (NDMA), which is classified as carcinogenic to humans. After the discovery, European medical agencies and the US Food and Drug Administration withdrew affected valsartan products from the market.

WHAT THIS STUDY ADDS

Among Danish valsartan users, exposure to NDMA contaminated valsartan was not associated with a markedly increased risk of overall cancer (adjusted hazard ratio 1.09, 95% confidence interval 0.85 to 1.41).

Future studies are, however, required to evaluate the risks for single cancer outcomes as well as long term effects.

Methods

We conducted a cohort study comparing cancer outcomes in users of potentially NDMA contaminated valsartan products with users of valsartan products assumed free from this contaminant.

Data sources and linkage

We obtained data from four Danish nationwide registries: the Danish Cancer Registry,^{8,9} the National Prescription Registry,¹⁰ the National Patient Register,¹¹ and the Civil Registration System.¹² Supplementary appendix A describes the data sources in detail and appendix B provides the codes for cancer diagnoses, drug exposures, and covariates. Data were linked by the personal identification number, a unique identifier assigned to all Danish residents since 1968.¹³ Virtually all medical care in Denmark is provided by the national health authorities, allowing population based register linkage studies covering all legal residents of Denmark.

Study cohort

The study cohort comprised all Danish patients filling a valsartan prescription during the study period of 1 January 2012 to 30 June 2018. Prevalent users of valsartan at the start of the study period—defined as individuals having filled a valsartan prescription in September to the end of December 2011, entered the study cohort at 1 January 2012, whereas incident users entered the study cohort at the day of filling their first valsartan prescription during the study period. As patients contributed risk time from one year after entering the study cohort, we excluded those with less than one year of follow-up, as they did not contribute to any of the analyses reported. For the same reason, we excluded incident users filling their first prescription after 30 June 2017. We further excluded patients with a record of a previous cancer except non-melanoma skin cancer; those with a recent migration before cohort entry (within two years) to ensure enough baseline data on all study participants; and those aged less than 40 years at cohort entry as both use of valsartan and cancer occurrence is rare among children and younger adults. Participants were followed until a cancer outcome, death, migration, or end of the study period (30 June 2018), whichever occurred first.

Ascertainment of NDMA exposure

Within the study cohort we mapped out each participant's exposure to NDMA contamination using the unique drug ID (Nordic article number) as recorded in the National Prescription Registry to identify the single valsartan product and its manufacturer. From the 128 unique valsartan drug products used during 2012-18 within our study population, we identified 18 drug products (which constituted 18% of all prescriptions filled) that were manufactured using an active pharmaceutical ingredient from Zhejiang Huahai Pharmaceuticals. These drug products were classified as probably contaminated with NDMA. An additional 36 drug products (26% of all prescriptions) were classified as possibly contaminated with NDMA,

as they contained an active pharmaceutical ingredient both from Zhejiang Huahai Pharmaceuticals and from other companies. Seventy four drug products (55% of all prescriptions) were classified as unlikely to be contaminated with NDMA as they did not contain an active pharmaceutical ingredient from Zhejiang Huahai Pharmaceuticals. In the main analysis we pooled together valsartan prescriptions classified as probably and possibly contaminated with NDMA, classifying those filling such prescriptions as ever exposed to NDMA from their first occurrence of such a prescription. We further stratified NDMA exposed person time by cumulative dose from filled prescriptions of potentially NDMA containing valsartan tablets (applying preplanned strata of <20 000, 20 000-49 999, and ≥50 000 mg). The use of milligrams of valsartan as a scale for the dose-response analysis was based on the observation that the NDMA content for each tablet seems to correlate with the strength of the tablet.¹⁴ With an estimated daily use of 80-160 mg (the defined daily dose of valsartan is 80 mg¹⁵), these cut-offs corresponded roughly to <200, 200-499, and ≥500 tablets. Of note, individuals classified as exposed to NDMA contributed follow-up to the non-exposed cohort until filling their first prescription for a potentially NDMA contaminated product. This ensured that the estimates were not affected by immortal time bias.¹⁶

Throughout all assessments of potential exposure to NDMA, we applied a one year lag time—that is, persons contributed NDMA exposed person time from one year after having filled their first prescription for a potentially NDMA containing valsartan product and onwards. This was done as very recent NDMA exposure (<1 year) is considered unlikely to materially affect an individual's risk of receiving a cancer diagnosis.¹⁷ The length of the lag time was subjected to sensitivity analyses.

Cancer outcomes

We obtained cancer outcomes from the Danish Cancer Registry.^{8,9} However, as data in this registry is currently only updated to 2016, we used the Danish National Patient Registry¹¹ to ascertain outcomes from 1 January 2017 to 30 June 2018. The primary outcome was a composite endpoint comprising all cancers (except non-melanoma skin cancer), as NDMA exposure is suspected to increase the risk of several different cancers. In supplementary analyses, we determined the risk of individual cancers, grouping cancers by organ system (ie, using codes from the international classification of diseases, 10th revision).

Covariates

The study cohort was described according to several characteristics that were also incorporated as covariates in the analyses: use of drugs (prescription fill <120 days before cohort entry) known or suspected to affect cancer risk, including low dose aspirin, non-aspirin non-steroidal anti-inflammatory drugs, 5-α reductase inhibitors, statins, spironolactone, oral

steroids, hormone replacement therapy, and selective serotonin reuptake inhibitors¹⁸; prior diagnoses (within five years from cohort entry) of diabetes, chronic obstructive pulmonary disease, heart failure, and alcohol related disease; Charlson comorbidity index scores (0, low; 1-2, medium; or ≥ 3 , high; based on diagnoses established within the past five years before cohort entry)^{19 20}; and whether the participant was a prevalent valsartan user at the beginning of the study period or initiated valsartan during the study period.

Main analysis

The primary analysis comprised a comparison of cancer occurrence during follow-up exposed to NDMA versus follow-up not exposed to NDMA. We used Cox regression to estimate the hazard ratio with 95% confidence intervals for cancer associated with NDMA exposure, both for ever use and for the predefined categories of cumulative use. The proportional hazards assumption was tested using Schoenfeld residuals. We carried out a formal dose-response test by categorising cumulative exposure to NDMA contaminated valsartan in categories of 10 000 mg as a time varying exposure and obtaining the P value for this variable as a continuous predictor of cancer risk in a Cox regression. As all comparisons were performed within users of valsartan, the exposure to NDMA can reasonably be expected to be a random event, and confounding is thus expected to be limited. Analyses were, however, performed as crude comparisons adjusted only for sex and age (age at cohort entry as continuous variable) as well as adjusted for sex, age, and the potential confounding factors. All analyses were performed using STATA Release 15.2.

Sensitivity and supplementary analyses

We carried out several sensitivity and supplementary analyses. Firstly, we performed analyses stratifying all participants by sex and age (40-69 and ≥ 70 years at cohort entry). Secondly, we restricted the cohort to prevalent valsartan users at the start of the study and to incident users during the study period. Thirdly, we restricted the ascertainment of NDMA exposure to prescriptions classified as probably contaminated with NDMA, while censoring individuals filling a prescription for a possibly NDMA contaminated drug product from the reference cohort (although allowing them to later enter the NDMA exposed cohort). Lastly, we varied the one year lag time period applied in the main analysis to six months and two years.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing of results. There are no plans to disseminate the results of the research directly to the patient community. However, the results will be included in the ongoing review of the potential

impact of NDMA contaminated valsartan on patients by the European Medicines Agency.

Results

In initial descriptive analyses, we identified 7068 unique individuals filling a total of 95 650 valsartan prescriptions from January 2012 to June 2018, the period where NDMA contaminated products were on the Danish market. The overall use of valsartan increased slightly during this period, in particular in 2017 and 2018 (fig 1), and the use of valsartan products possibly or probably contaminated with NDMA constituted about half of the total valsartan use, although this proportion dropped slightly during 2017-18.

For the selection of the study cohort, we identified 6406 individuals filling a valsartan prescription between September 2011 and June 2017. Of these, 5150 unique individuals met our inclusion criteria and entered the final cohort (fig 2), contributing a median of 4.6 years (interquartile range 2.0-5.5 years) of follow-up to the analysis, after the application of a one year lag period. Table 1 includes the baseline characteristics of valsartan users entering the study. A total of 3625 participants contributed 7344 person years of follow-up classified as unexposed to NDMA, and 3450 participants contributed 11 920 person years classified as ever exposed to NDMA (fig 2). The distribution of potentially NDMA contaminated and non-contaminated prescriptions were similar between the study cohort and all valsartan users (see supplementary figure 1).

Overall, exposure to potentially (probably or possibly) NDMA contaminated valsartan products showed no association with cancer compared with exposure to valsartan products unlikely to be contaminated with NDMA (adjusted hazard ratio 1.09, 95% confidence interval 0.85 to 1.41) and no evidence of a dose-response relation ($P=0.70$, table 2).

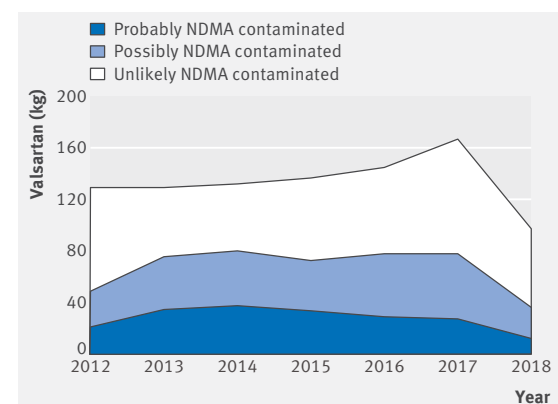


Fig 1 | Use of valsartan in kilograms of active substance, specified by drug products classified as probably, possibly, or unlikely to be contaminated with N-nitrosodimethylamine (NDMA). The drop in 2018 results from data only being available to June 2018

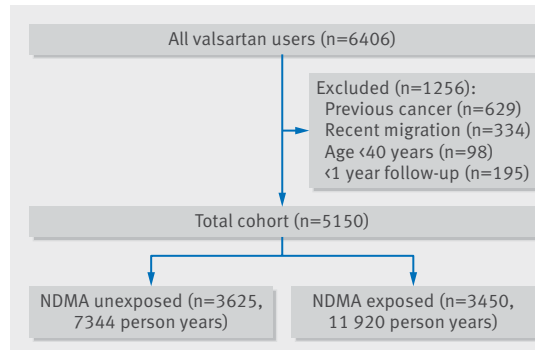


Fig 2 | Flowchart of cohort selection of Danish users of valsartan, January 2012 to June 2018. NDMA=N-nitrosodimethylamine

In analyses of single cancer outcomes, increased risks were seen for colorectal cancer (hazard ratio 1.46, 95% confidence interval 0.79 to 2.73) and for uterine cancer (1.81, 0.55 to 5.90), although neither these nor other single cancer outcomes reached statistical significance (fig 3). Analyses of other cancer outcomes were not possible owing to low numbers—that is, no cancer outcomes outside those included in figure 3 showed any associations with NDMA use.

Results comparable to the main analyses were found when we stratified by sex and age, whereas a

stronger association was seen when we restricted to incident users during the study period (hazard ratio 1.58, 95% confidence interval 0.99 to 2.52) compared with prevalent users at the beginning of the study period (0.91, 0.66 to 1.25) (fig 4). A test for interaction between being an incident valsartan user and the effect of exposure to NDMA yielded a p value of 0.059.

The sensitivity analysis censoring individuals filling a prescription for a possibly NDMA contaminated valsartan product from the reference category yielded results comparable to those of the main analyses, both for overall cancer (see supplementary table 1) and for single cancers (see supplementary figure 2).

Varying the lag time from one year used in the main analyses to six months or two years yielded slightly higher risk estimates with increasing lag time, with the hazard ratio for ever exposure increasing to 1.17 (95% confidence interval 0.88 to 1.55) when a two year lag time was applied, although this did not reach statistical significance (see supplementary table 2).

Discussion

In this nationwide cohort study of Danish valsartan users, we did not see an increased short term overall risk of cancer associated with the use of valsartan products potentially contaminated with N-nitrosodimethylamine (NDMA).

Table 1 | Baseline characteristics of valsartan users entering study and among those potentially exposed and not exposed to N-nitrosodimethylamine (NDMA)

Characteristics	All (n=5150)	NDMA exposure	
		Exposed* (n=3450)	Not exposed* (n=3625)
Sex:			
Men	2531 (49.1)	1630 (46.9)	1745 (43.6)
Women	2619 (50.9)	1820 (53.1)	1880 (56.4)
Age (years):			
Median (interquartile range)	66 (58-74)	-	-
40-69	3195 (62.0)	2197 (65.0)	2164 (61.2)
≥70	1955 (38.0)	1253 (35.0)	1461 (38.8)
Prevalent valsartan users†:			
No	2870 (55.7)	2012 (51.2)	1353 (25.7)
Yes	2280 (44.3)	1438 (48.8)	2272 (74.3)
Charlson comorbidity score:			
0 (low)	3864 (75.0)	2697 (79.0)	2635 (74.9)
1	884 (17.2)	541 (15.3)	670 (17.1)
2	217 (4.2)	117 (3.2)	168 (4.5)
≥3 (high)	185 (3.6)	95 (2.5)	152 (3.4)
Drugs:			
Low dose aspirin	1388 (27.0)	842 (25.2)	1092 (29.2)
Non-aspirin NSAID	772 (15.0)	533 (15.5)	513 (16.0)
Statins	1924 (37.4)	1185 (35.1)	1457 (37.4)
Spironolactone	405 (7.9)	117 (3.2)	362 (4.9)
Glucocorticoids for systemic use	244 (4.7)	166 (4.5)	171 (4.3)
5-α reductase inhibitors	64 (1.2)	41 (1.2)	47 (0.9)
SSRIs	299 (5.8)	196 (5.7)	223 (6.0)
Hormone replacement therapy	454 (8.8)	319 (9.8)	338 (9.9)
Diagnoses:			
Diabetes type 1 and 2	899 (17.5)	559 (16.1)	667 (18.0)
Chronic obstructive pulmonary disease	247 (4.8)	131 (3.5)	200 (4.3)
Congestive heart failure	535 (10.4)	117 (2.9)	497 (5.3)
Alcohol related disease	48 (0.9)	28 (0.7)	34 (0.7)

NSAID=non-steroidal anti-inflammatory drug; SSRIs=selective serotonin reuptake inhibitors.

*Characteristics weighted by proportion of total time exposed or not exposed that individuals contributed, thereby providing the distribution of covariates in the main analysis comparison.

†Defined as being included in the study at 1 January 2012 by having filled a valsartan prescription between September and December 2011.

Table 2 | Estimates for association between use of valsartan products potentially contaminated with N-nitrosodimethylamine (NDMA) and cancer risk compared with non-contaminated valsartan products

NDMA exposure	Follow-up (person years)	Cancer outcomes	Incidence rate (/1000 person years)	Adjusted hazard ratio* (95% CI)	Fully adjusted hazard ratio† (95% CI)
Never use	7344	104	14.2	1.00 (ref)	1.00 (ref)
Ever exposure	11 920	198	16.6	1.16 (0.91 to 1.49)	1.09 (0.85 to 1.41)
Cumulative exposure (mg)‡:					
<20 000	3776	67	17.7	1.26 (0.92 to 1.72)	1.15 (0.83 to 1.59)
20000-49 999	2836	44	15.5	1.07 (0.75 to 1.53)	0.99 (0.69 to 1.43)
≥50 000	5308	87	16.4	1.14 (0.84 to 1.54)	1.11 (0.82 to 1.50)
Test for trend§				P=0.65	P=0.70

*Adjusted for age and sex.

†Adjusted for sex, age, use of low dose aspirin, non-aspirin non-steroidal anti-inflammatory drugs, 5- α reductase inhibitors, statins, spironolactone, oral steroids, hormone replacement therapy, or selective serotonin reuptake inhibitors, history of diabetes, chronic obstructive pulmonary disease, heart failure, or alcohol related disease, Charlson comorbidity index score, and being a prevalent valsartan user.

‡Defined by total amount of NDMA contaminated valsartan filled.

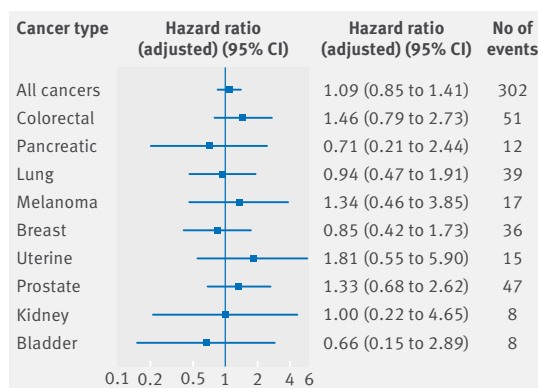
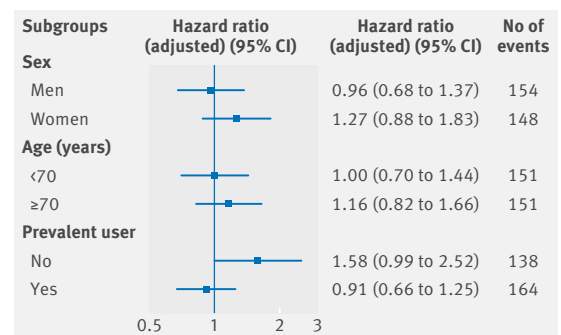
§Estimated using Cox regression across 10 000 mg strata of NDMA contaminated valsartan filled.

Strengths and limitations of this study

The principal strength of this study is the use of high quality nationwide registries,^{9 10 11} leaving little potential for selection bias.¹² Furthermore, the use of dispensing data, instead of data on prescribed drugs, as a proxy for NDMA exposure reduces the risk of misclassification due to primary non-adherence.²¹ The principal weakness of the study is the limited median follow-up. Our findings only pertain to early cancer risk after exposure to NDMA whereas future studies are needed to elucidate the total cancer risk, which requires a substantially longer follow-up for the individual than what is currently available. Additionally, the limited follow-up combined with the low use of valsartan in Denmark leads to limited precision. Lastly, our exposure ascertainment is based on assumptions about NDMA content. Reassuringly, our sensitivity analysis disregarding less certain sources of NDMA returned estimates comparable to those of the main analysis. However, future studies should utilise data on the actual NDMA content of individual valsartan tablets once such information becomes available.

Biological rationale

The International Agency for Research on Cancer (IARC) has classified NDMA as “probably carcinogenic to humans” owing to limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animal studies.⁷ NDMA is suspected to have both localised and systemic carcinogenic effects due to the induction of DNA-damaging metabolites in the gastrointestinal tract and liver.^{6 22} Specifically, in the liver, NDMA is metabolised by CYP2E1 to methyldiazonium, which causes mutations by methylation.²³ Also, N-nitroso compounds such as NDMA activate *ras* oncogenes, which are thought to play a role in the development of colon cancer.⁶ As such, tumours in the gastrointestinal tract, lungs, kidneys, and liver have been seen in animal studies.^{5 23 24} Evidence of carcinogenicity in rats was found at doses of about 10 $\mu\text{g/kg/day}$.²³ With concentrations of up to 22 μg NDMA in 320 mg valsartan tablets and 10 μg NDMA in 160 mg tablets,¹⁴ the daily exposure for a 70 kg person ranges from 0.14 to 0.31 $\mu\text{g/kg/day}$. Even though it is not possible to extrapolate directly from animals to humans, the daily exposure in humans is thus roughly 30 times lower than the lowest dose leading to liver cancer in rats. Owing to the known carcinogenic effect of NDMA in animals,

**Fig 3 | Estimates for association between use of potentially N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of single cancer outcomes compared with users of non-contaminated valsartan products. Number of events are total number of events among valsartan users****Fig 4 | Estimates for association between use of potentially N-nitrosodimethylamine (NDMA) contaminated valsartan products and cancer risk compared with users of non-contaminated valsartan products, specified by patient subgroups. Number of events are total number of events among valsartan users**

no experimental studies in humans exist. However, as some dietary products (eg, processed meat) are known to contain small amounts of NDMA, epidemiological studies based on food frequency questionnaire data have been performed. Even though such studies are highly prone to confounding, three found an increased risk of gastrointestinal cancer with exposure to NDMA, predominantly colorectal cancer.^{25 26 27} This finding, together with that from the animal studies, provides some support for the increased although statistically non-significant risk for this particular cancer observed in our study. Only one previous paper has reported on uterine cancer, finding no association between exposure to NDMA and uterine cancer in rats.²⁸ Lastly, no estimates could be obtained for liver cancer in our study owing to the absence of liver cancer events among those exposed to NDMA. A markedly increased risk of liver cancer associated with NDMA exposure thus seems unlikely.

Principal findings

Our estimates pertain to early cancer risk associated with exposure to NDMA through contaminated valsartan products and should not be interpreted as evidence against NDMA being carcinogenic to humans in general. At most, our findings suggest that the levels of NDMA exposure achieved through valsartan products do not translate into a substantially increased short term cancer risk. Furthermore, the fact that our study evaluates a potential safety concern holds some implications about how to interpret the results. While the estimate for our primary outcome suggests a negligible and statistically non-significant increase in cancer risk of 9%, it might be argued that a more cautious interpretation, reflecting the nature of the study question, would be to consider the upper limit of the confidence interval. Doing so leads to the different, although related, conclusion that we can reasonably exclude a more than 40% increased short term risk of cancer from exposure to NDMA contaminated valsartan products. A similar interpretation of the estimates obtained for the single cancer outcomes—in particular colorectal and uterine cancer—clearly highlights that our study cannot confidently rule out an increased risk from exposure to NDMA.

The finding that exposure to NDMA was associated with an increased risk of cancer specifically among users initiating valsartan treatment during the study period, as opposed to among valsartan users prevalent at the beginning of the study period, was a surprising finding that we cannot explain. The duration of follow-up was on average longer for prevalent users, as they were followed from the beginning of the study period (1 January 2012), and a late effect of exposure to NDMA therefore cannot explain this finding, as it would have led to an increased risk specifically among prevalent and not incident valsartan users. Considering the uncertainty about the actual NDMA content of valsartan products, it could be speculated that those using valsartan later in the study period might have been exposed to NDMA more often. However, no data

are available that can be used to test this hypothesis. Lastly, our subgroup analyses had limited power and therefore the possibility of our results being a chance finding should also be considered.

Policy implications

Our findings can support regulators in their evaluation of the potential public health impact of exposure to NDMA through valsartan products. The Danish nationwide health registries and the strong research infrastructure hosted by Statistics Denmark and the Danish Health Data Authority, the latter of which was used in this study, gives researchers and regulators a unique possibility to provide answers to such emerging public health concerns in a timely manner. The present analysis was completed and submitted for publication within seven weeks after the finding of NDMA in valsartan products was announced publicly, and the paper published in *The BMJ* after a fast track peer review process spanning only three weeks from submission to publication. We previously performed a similar expedited assessment of a putative bleeding risk associated with use of generic warfarin,^{29 30} although its publication was delayed by the peer review process for several months. Besides rapid peer review assessment, a close collaboration between researchers and regulators is a key element in ensuring both speed and relevance of such research projects. In addition to knowledge about the risks associated with exposure to NDMA, the present study provides proof-of-concept for such processes, which hold great promise for the use of pharmacoepidemiological input in the regulatory assessment of future public health crises.

Conclusion

We have assessed the potential cancer risk associated with exposure to NDMA through contaminated valsartan products and found no evidence of a markedly increased short term overall risk of cancer. However, we cannot exclude a modest association. Furthermore, owing to the limited follow-up, assessment of long term effects was not possible, and the low number of events makes interpretation of estimates for single cancer outcomes difficult. Therefore, further studies are needed to fully elucidate the health effects of NDMA contaminated valsartan products.

We thank the Danish Health Data Authority, in particular Anna Birkmose Andersen and Anders Schierup, for providing expedited access to the registry data used in the study; Nicolai C Brun (Danish Medicines Agency) for valuable comments on the interpretation of the findings; and Camilla Ærtebjerg Bæk (Danish Medicines Agency) for providing toxicological input.

Contributors: AP, JH, PQ, and NB conceived and designed the study. AP, KBK, and MTE performed the statistical analyses and data management. AP and KBK drafted the initial manuscript. All authors interpreted the data and revised the manuscript critically. AP is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: None.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial

relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: Statistical code is available from AP upon request. No additional data are available as Danish legislation does not allow disclosure of individual level data.

Transparency: The lead author (AP) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Supplementary information: appendices A and B

Exhibit N

Int. J. Cancer: 66, 130–134 (1996)

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Publication of the International Union Against Cancer
Publication de l'Union Internationale Contre le Cancer

N-NITROSODIMETHYLAMINE-DERIVED O⁶-METHYLGUANINE IN DNA OF MONKEY GASTROINTESTINAL AND UROGENITAL ORGANS AND ENHANCEMENT BY ETHANOL

Lucy M. ANDERSON^{1,4}, Vassilis L. SOULIOTIS², Saranjit K. CHHABRA¹, Thomas J. MOSKAL³, Steven D. HARBAUGH³ and Soterios A. KYRTOPOULOS²

¹Laboratory of Comparative Carcinogenesis, NCI, Frederick, MD; ²National Hellenic Research Foundation, Athens, Greece; and ³BioQual, Inc., Rockville, MD.

N-nitrosodimethylamine (NDMA) is a human cancer initiator suspect. Ethanol, a cancer risk factor, may synergize with nitrosamines by suppressing hepatic clearance, to increase internal exposure. A limitation to these hypotheses is lack of activation of NDMA by many rodent tissues. However, systematic primate studies are lacking. Patas monkeys were utilized to investigate NDMA activation by primate tissues *in vivo*, generating the promutagenic DNA lesion O⁶-methylguanine (O⁶-meG). Adult monkeys received 0.1 mg/kg NDMA by gavage, in some cases preceded by ethanol. Four hours after NDMA only, O⁶-meG was detected in DNA from all tissues. Levels were highest in gastric mucosa and liver and were only about 50% lower in DNA from white blood cells, esophagus, ovary, pancreas, urinary bladder and uterus. With ethanol co-exposure, amounts of O⁶-meG increased at least 2-fold in all tissues except liver. The largest effect was in esophagus (17-fold increase), followed by ovary, large intestine, urinary bladder, spleen and cerebellum (9- to 13-fold increases), and uterus, cerebrum and brain stem (7- to 8-fold increases). Alkylguanine alkyltransferase activities varied over a 30-fold range and were highest in liver and stomach. Thus primate tissues, especially those of the gastrointestinal and urogenital organs, are sensitive targets for DNA adduct damage due to NDMA, and ethanol co-exposure leads to striking increases in adducts. Our data support epidemiology implicating nitrosamines in causation of cancers of stomach and other organs, and alcohol as enhancing internal exposure to nitrosamines.

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Nitrosamines, which are potent carcinogens in experimental animals and ubiquitous environmental agents, have been long suspected as contributors to human cancer risk (Magee, 1989; Mirvish, 1995). In particular, attention has been given to their participation in causation of smoking-related cancers of upper aerodigestive tract, lung, pancreas, kidney, urinary bladder and large bowel; cancers of the stomach related to dietary nitrosamines and/or intragastric nitrosation; and neoplasms of several of these organs associated with infection by microbes with nitrosating capacity (Magee, 1989; Mirvish, 1995). Epidemiological confirmation of these hypotheses has been difficult, since occurrence of nitrosamines is both widespread and associated with complex mixtures. A role for the most commonly found nitrosamine, N-nitrosodimethylamine (NDMA), in most of these cancers has been questioned, because of lack of ability of the corresponding tissues in rodents to activate it to a DNA-damaging form, and absence of tumors in these rodent organs after *in vivo* exposure (Labuc and Archer, 1982; Von Hofe *et al.*, 1987).

However, it has been uncertain whether similar limitations pertain to humans. Human tissues have been shown to metabolize NDMA (Harris, 1987), but the meaning of this with regard to *in vivo* effects has been unclear. We have therefore utilized a non-human primate model, the patas monkey, to determine relative levels of a promutagenic DNA adduct formed *in vivo* by NDMA, O⁶-methylguanine (O⁶-meG). The important contribution of such alkyl DNA adducts to cancer etiology has been evidenced by recent demonstrations of protective effects of overexpression of the enzyme that repairs

them, alkylguanine alkyltransferase (Gerson *et al.*, 1994), and by demonstration in humans of alkylation of DNA in gastrointestinal tissues (Hall *et al.*, 1991) and of association between levels of O⁶-meG in leukocytes and geographical prevalence of gastric cancer (Forman *et al.*, 1994).

NDMA, at low *in vivo* concentrations, is activated primarily by cytochrome P450 2E1 in all species, including humans (Yang *et al.*, 1990). Previously, we observed that patas monkey liver contains P450 2E1 with a molecular size and NDMA demethylase activity similar to those of humans (Anderson, 1992). A pharmacokinetic study indicated that a high percentage of NDMA clearance in patas monkeys could be extrahepatic (Gombar *et al.*, 1990), in contrast to rodents, where metabolism occurs almost exclusively in liver, and with obvious implications regarding potential genotoxic damage in extrahepatic organs.

A related human cancer risk issue is the mechanism of risk enhancement by consumption of alcoholic beverages. Such consumption greatly increases the risk of cancers of the liver and upper aerodigestive tract, and in the case of the latter tissues, further strongly synergizes with tobacco use (Blot, 1992). A number of hypotheses have been put forward to explain this effect of ethanol and/or the congeners in beverages, ranging from solubilization effects, enhancement of cellular entry of carcinogens and inhibition of DNA repair, to tumor promotion (Seitz *et al.*, 1992; Blot, 1992; Mufti, 1992). We and others have noted that, thus far, the largest and most consistent *in vivo* effect of ethanol yet described is enhancement of exposure of internal organs to nitrosamines caused by ethanol-mediated inhibition of first-pass hepatic clearance (Swann *et al.*, 1984; Anderson, 1992; Anderson *et al.*, 1995).

Thus, in mice, ethanol given simultaneously with a single oral dose of NDMA caused 8- to 10-fold increases in the area-under-the-blood-concentration-vs.-time curve (AUC, the best measure of internal exposure), in levels of O⁶-meG in lung DNA, and in number of lung tumors (Anderson, 1992; Anderson *et al.*, 1995). The effect was also seen after chronic dosing in drinking water, was cumulative over a long time course, and eventually involved kidney as well as lung. Absence of an effect on tumorigenesis, when the ethanol and NDMA did not reach the liver simultaneously, confirmed the suppression-of-clearance mechanism.

A similar profound effect of ethanol on clearance of NDMA was also demonstrated in patas monkeys, at blood levels of ethanol comparable to those achieved in humans (Anderson *et al.*, 1995). After an ethanol dose of 1.6 g/kg, clearance of 1 mg/kg NDMA was completely suppressed for at least 6 hr. At approximately the same blood ethanol levels, the increases in AUC for NDMA were similar in monkeys and mice. It was

⁴To whom correspondence and reprint requests should be addressed, at the Laboratory of Comparative Carcinogenesis, NCI, Building 538, FCRDC, Ft. Detrick, Frederick, MD 21702.

therefore of interest to determine whether the increased exposure of the internal organs would result in increased alkylation of DNA in monkeys, as in mice.

MATERIAL AND METHODS

Male and female *Erythrocebus patas* monkeys were maintained under conditions approved by the American Association for Accreditation of Laboratory Animal Care; they were 4 to 12 years old and weighed 5–6 kg (females) or 12–13 kg (males). Some of the monkeys used in this study had been exposed to carcinogens, but none within the previous 5 years. The inter-monkey reproducibility of the data confirmed that these earlier treatments did not affect the outcome of the present experiments. The monkeys were trained to accept oral administration of chemicals without anesthesia, by use of physical restraint and treat reward. NDMA (Sigma, St Louis, MO) was administered in sterile water (2 ml/kg), by gavage. Ethanol was given 45 min before the NDMA, 1.6 g/kg (8 ml/kg of a 20% solution), also by gavage.

In Series I, 3 female monkeys were used for blood collection only, and they each were treated in 4 sequential experiments, at 2 week intervals, with 0.1 mg/kg NDMA; this dose plus ethanol; 1 mg/kg NDMA; and the latter NDMA dose plus ethanol. Blood samples were centrifuged at 2,500 rpm for 30 min and the cell fraction frozen.

In Series II, 7 monkeys were treated and killed for collection of tissues, 5 with NDMA (0.1 mg/kg, 3 females, 2 males) or 2 with ethanol/NDMA (2 females). In view of the between-monkey reproducibility of the data, it was decided that 2 monkeys were sufficient for the latter treatment, in keeping with the general policy to utilize as few monkeys as possible. For 2 females of each treatment group, 2 ml of blood was drawn at 20 min, 40 min, and 2 hr. All were killed at 4 hr by treatment with a high dose of ketamine, followed by exsanguination; organs were removed as rapidly as possible and placed on wet ice for dissection and separation of mucosal surfaces, and tissue pieces were frozen at -80°C . Assays for content of $\text{O}^6\text{-meG}$ in DNA and for alkylguanine alkyltransferase (AGT) were as described previously (Souliotis and Kyrtopoulos, 1989; Souliotis *et al.*, 1990).

For the time course of change in level of DNA adducts in blood cells, similar results were obtained by averaging values from all the monkeys (Series I and II) and by comparing different experimental treatments of the same monkey (Series I). Therefore only the former data are shown (Fig. 2).

RESULTS

DNA alkylation data were obtained for 32 types of monkey tissues. The repair enzyme AGT was measured in many of these tissues in a separate monkey, and the results are given in the figure legends and Table I. The AGT values are in good agreement with those reported for comparable *Macaca cynomolgus* monkey and human tissues (Hall *et al.*, 1985; Loktionova *et al.*, 1993). Amounts of AGT varied over a 30-fold range in the monkey tissues.

Gastrointestinal tract

Striking findings were obtained (Fig. 1a). First, after administration of NDMA only, adduct levels in stomach mucosa were similar to, indeed consistently slightly higher than, those in liver; these were the highest levels of all tissues, in each of the 5 monkeys tested. $\text{O}^6\text{-meG}$ levels in mucosa of esophagus, pancreas, large bowel and small bowel ($1.0 \pm 0.2 \mu\text{mol/mol G}$), were also within 50% of those in liver. It is evident that, in apparent contrast to rodents, these important cancer targets share with liver an equivalent likelihood of sustaining DNA damage after NDMA exposure.

TABLE I. – DNA ADDUCTS AND AGT IN OTHER TISSUES¹

Tissue	$\text{O}^6\text{-meG}$ ($\mu\text{mol/mol G}$)		AGT (fmol/ μg DNA)
	NDMA	Ethanol/NDMA	
Bone marrow	0.5 ± 0.2	1.3 ± 0.2	7.10
Spleen	0.4 ± 0.2	5.3 ± 0.5	16.30
Lymph nodes	0.1 ± 0.04	NT	5.14
Prostate	0.3 ± 0.1	NT	NT
Adrenal	0.3 ± 0.1	1.5 ± 0.3	3.92
Pituitary	0.2 ± 0.1	NT	NT
Salivary gland	0.2 ± 0.02	NT	4.55
Skeletal muscle	0.2 ± 0.1	0.8 ± 0.2	2.38
Heart muscle	0.4 ± 0.1	2.1 ± 0.5	2.97
Heart endothelium	0.3 ± 0.1	1.9 ± 0.5	NT
Skin	0.3 ± 0.1	0.8 ± 0.2	4.80
Lung, peripheral	0.1 ± 0.03	0.5 ± 0.1	14.64
Lung, bronchus	0.08 ± 0.01	0.4 ± 0.1	10.13

¹NT, not tested.

Secondly, co-exposure to ethanol resulted in marked increases in the level of $\text{O}^6\text{-meG}$ adduct in esophageal mucosa (17-fold), colon mucosa (11.9-fold) and pancreas (6.4-fold). A much smaller effect was seen in stomach (2.1-fold). There was no effect in liver, which was the only tissue for which no enhancement by ethanol was seen.

Greatest amounts of AGT were present in liver and stomach and 50% less in pancreas and large and small intestines. Esophageal AGT was about 25% that in stomach.

Urogenital tract

After NDMA only, urinary bladder, ovary and uterus presented amounts of DNA adducts that were again within 50% of those in liver (Fig. 1b). Levels were lower in the kidneys and were greater in the right kidney in 4 of the 5 monkeys ($p = 0.018$, paired two-tailed t test). Interestingly, the right kidney had about 30% less AGT activity. Amounts of adduct in right and left testes were similar, $0.5 \pm 0.1 \mu\text{mol/mol G}$.

Ethanol co-exposure greatly increased the amounts of DNA adducts in all of these tissues, 10.9-fold for urinary bladder, 4- to 5-fold for kidney, 7.8-fold for uterus and 9.4-fold for ovary.

Kidney, ovary and uterus had intermediate levels of AGT, about 30–40% that of liver, whereas bladder AGT was 10–12% of liver.

Nasal cavity mucosa and brain

Adduct levels were similar in all these tissues after NDMA only and were about 20% those in liver (Fig. 1c). Oral mucosa adduct levels were similar, $0.3 \pm 0.1 \mu\text{mol/mol G}$. Ethanol treatment resulted in a 5.1-fold increase in adducts of nasal cavity mucosa DNA, 7- to 8-fold increases in cerebrum and cerebellum and a 10-fold elevation in the brain stem. AGT values in the 3 areas of brain were low, 3–8% of liver.

White blood cells and other tissues

Sequential sampling of blood at intervals after dosing with 0.1 mg/kg NDMA showed that adduct levels in white blood cells were already maximum at 20 min and decreased thereafter, with apparent biphasic repair (Fig. 2a). In the presence of ethanol, adduct levels were 1.5- to 2-fold greater throughout this course. With the higher dose of 1 mg/kg, adduct levels were more than 10-fold greater than with 0.1 mg/kg (Fig. 2b). The ethanol effect and the adduct loss curves were similar to those obtained with the lower NDMA dose.

Data for other tissues tested are presented in Table I. These had adduct levels that were 10–20% of those in liver and showed in general a 3- to 6-fold effect of ethanol, except for spleen, where a 12.6-fold increase was noted. AGT levels were moderate in spleen and lung, and low in the other tissues tested.

DISCUSSION

The results of our study with a non-human primate model provide confirmation of 2 hypotheses regarding a possible role for nitrosamine in human carcinogenesis. The first hypothesis

is that nitrosamines present in food, beverages or tobacco-related products, or those formed *in vivo* by spontaneous or microbe-catalyzed nitrosation, could initiate cancers in a spectrum of human tissues. We have now shown that, after oral administration of a low dose of NDMA to monkeys, a promutagenic DNA adduct was present, at levels similar to those in liver, in many of these target tissues: esophagus, stomach, pancreas, large bowel, urinary bladder, uterus, ovary and white blood cells. Indeed, amounts of adducts in stomach mucosa were consistently higher than in liver. Therefore,

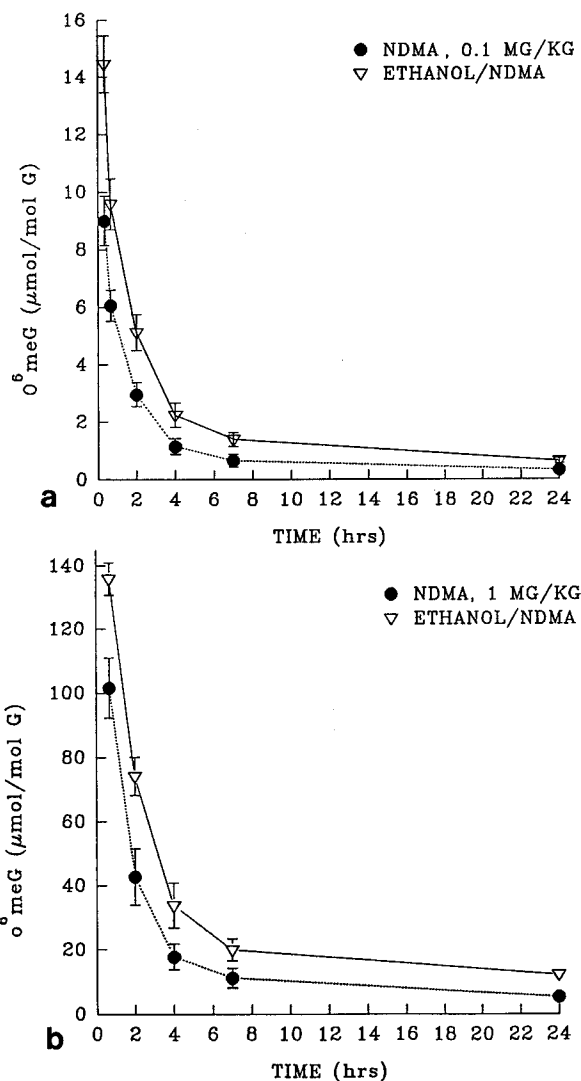
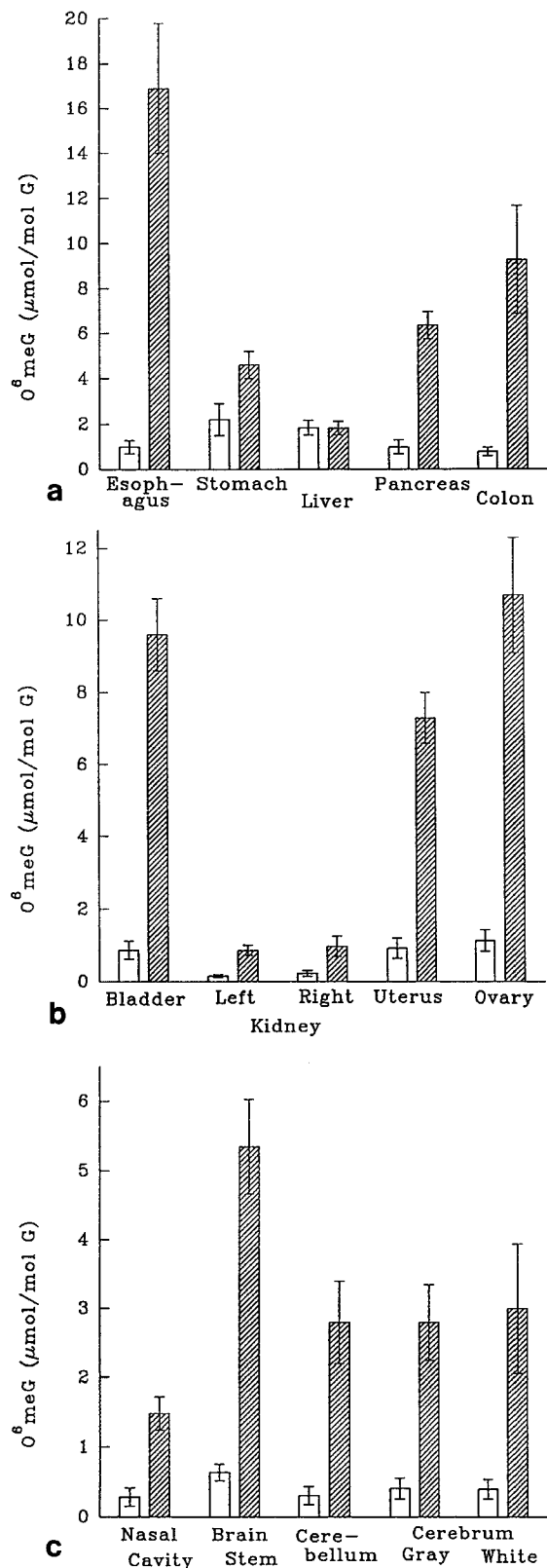


FIGURE 2 – O^6 -meG in DNA of blood cells taken at the indicated intervals after NDMA only (dotted line, closed circles) or ethanol/NDMA (solid line, open triangles). (a) NDMA at 0.1 mg/kg. (b) NDMA at 1.0 mg/kg. Values are the average of 2–5 samples \pm SD.

FIGURE 1 – O^6 -meG in DNA, average $\mu\text{mol/mol G} \pm$ SD. Open bars, NDMA only; hatched bars, ethanol/NDMA. (a) Gastrointestinal tissues. The levels of AGT as fmol/ μg DNA, measured in a separate female monkey, were: esophagus, 9.35; stomach, 37.84; liver, 47.42; pancreas, 20.14; colon, 19.87; small intestine, 18.90. (b) Urogenital tissues. AGT values were: bladder, 5.63; kidney, left, 19.45; kidney, right, 14.26; uterus, 4.34; ovary, 12.66. (c) Nasal cavity and brain. AGT values were: brain stem, 3.64; cerebrum, gray, 1.5; cerebrum, white, 2.31.

substantial DNA damage is sustained in these tissues, and tumors could be initiated.

The second hypothesis is that alcohol use increases the risk of certain cancers, at least in part by inhibiting hepatic clearance and thereby causing increased internal exposure. Our monkey study affirms this hypothesis, showing that co-exposure to ethanol resulted in large increases in DNA adducts in certain tissues. The change in esophagus was particularly striking, 17-fold, and matches closely the 18-fold increase in risk of human esophageal cancer that occurs with tobacco plus heavy alcohol use (Tuyns *et al.*, 1980). While this quantitative similarity may be coincidental, it does indicate that the suppression-of-clearance effect *could* by itself account for the elevation in risk. A number of other monkey tissues showed an 8-fold or greater change: cerebellum, brain stem, large bowel, spleen, urinary bladder, ovary and uterus.

Only the liver showed no enhancement of adducts after ethanol co-treatment. Similar findings have been reported for rats (Swann *et al.*, 1984) and mice (Anderson, 1992). Thus, this action of ethanol would not contribute to increased risk for liver cancer. Why the liver differs from the other tissues in this regard is unknown. Possibly, almost all of the activation and catabolism of NDMA in the liver is catalyzed by P450 2E1, which is, obviously, strongly inhibited by ethanol, so that increased exposure is exactly counterbalanced by decreased activation rate. In other tissues, one or more other P450s, or other enzymes, that are less sensitive to ethanol inhibition, may activate NDMA.

The various tissues clearly differed in both amount of DNA adduct present 4 hr after treatment with NDMA alone, and in relative effect of ethanol, and so were each actively influencing the outcome of exposure. In general, tissues with high adducts after NDMA only also showed a marked ethanol effect: esophagus, large bowel, urinary bladder, ovary and uterus. Apparent exceptions were the white blood cells, with a relatively high adduct level but a small ethanol effect, and spleen and cerebellum, characterized by relatively low adducts

but a large ethanol effect. Amounts of NDMA activating and DNA repair enzymes, and possible suicide-destructive effects of NDMA, as well as inhibitory effects of ethanol on these enzymes, might be expected to interplay uniquely in each tissue.

The relatively high level of adducts in blood cells is of interest, since these cells are used in human biomarker studies. The monkey data suggests that the blood cell values may predict rather closely the adduct levels in sensitive target organs. It was puzzling that adduct formation in the blood cells apparently reached a peak shortly after NDMA dosing and then rapidly declined even in the presence of ethanol. NDMA, at least after the 1 mg/kg dose, would have continued to circulate at maximum blood levels for more than 6 hr, until the suppression of hepatic clearance was relieved by elimination of the ethanol. It is possible that an ethanol-insensitive enzyme, with a relatively high K_m for NDMA, in intestinal mucosa or periportal cells of liver, was responsible for the initial activation leading to DNA adducts in the white blood cells. Further studies involving i.v. administration are planned to test this possibility.

The levels of the AGT repair enzyme tended, as might be expected, to be greatest in tissues that would interact directly with environmental chemicals: mucosa of the gastrointestinal tract, liver, kidneys and lung. The prominence of AGT in gastric mucosa, second in amount only to liver, further attests to the likelihood of alkylation damage in this tissue. The presence of high levels of O⁶-meG in gastric mucosa DNA 4 hr after treatment, in spite of abundant AGT, suggests that initial damage could have been much higher.

In conclusion, our monkey data support the hypotheses that nitrosamines contribute to cancer risk of the gastrointestinal and urogenital tracts, and that ethanol enhances risks of some of these cancers by suppressing first-pass hepatic clearance of nitrosamines. Further work is needed, particularly on the mechanisms of NDMA activation in tissues other than liver, which are important human cancer targets.

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Exhibit O

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Only the Westlaw citation is currently available.

NOT FOR PUBLICATION

United States District Court, D. New Jersey.

Jeff PLAYER, et al., Plaintiffs,

v.

MOTIVA ENTERPRISES LLC, a successor
in interest to Star Enterprises, Defendant.

No. Civ. 02-3216(RBK).

Jan. 20, 2006.

Attorneys and Law FirmsKeith A. McKenna, McKenna, Mulcahy & McKenna,
Montclair, NJ, for Plaintiffs.Jeffrey W. Moryan, Connell Foley LLP, Roseland, NJ, for
Defendant.**OPINION**

KUGLER, United States District Judge:

*1 This matter comes before the Court upon motions by Defendant Motiva Enterprises, LLC, ("Defendant" or "Motiva") for summary judgment of the claims of Plaintiffs Jeff Player, et al. ("Plaintiffs"), and to exclude Plaintiffs' experts Michael Gochfeld, M.D., Ph.D. ("Gochfeld"), R. Brian Ellwood, Ph.D. ("Ellwood"), Bruce M. Gallo ("Gallo"), and Daniel McDonald ("McDonald"). For the reasons set forth below, Defendant's motions will be granted in part and denied in part.

I. Background¹

This environmental contamination suit is brought by the current and former owners of twenty-seven parcels of residential property located in the Spring Hollow Subdivision in Gloucester Township, New Jersey.² Plaintiffs allege that emissions from Defendant's nearby Texaco gasoline service station contaminated their property and the Kirkwood Cohansey Aquifer, the underground water source for their potable wells.

Contamination of the aquifer was first detected on April 5, 2000, when significant concentrations of the gasoline-related compound methyl tertiary butyl ether ("MTBE") was discovered in a drinking fountain at Camden County Community College. New Jersey Consumers Water Company ("Consumers"), the entity responsible for providing water to the college, conducted sampling of some of its wells and discovered significant amounts of gasoline-related compounds in municipal supply well number 8 ("CW-8"). Consumers took the well offline on April 10.

While investigating the contamination, the New Jersey Department of Environmental Protection ("NJDEP") detected a discharge of volatile organic compounds ("VOCs") from Defendant's service station, located at 585 Berlin Cross Keys Road ("Motiva site" or "contamination site").³ The NJDEP issued a Field Directive on April 12, 2000, requiring Motiva to investigate the source and extent of the discharge, to implement an interim treatment system, and to submit a remedial action work plan to the NJDEP. Defendant installed an interim recovery system and twenty-five monitoring and recovery wells between April and June 2000.

The NJDEP issued a second directive on May 5, 2000, ordering Defendant to cease gasoline retail operations and provide treatment or an alternate source of water to replace CW-8. Defendant replaced the interim system with a permanent ground water recovery and treatment system in June 2000, and installed forty-one additional monitoring wells from June 2000 to present. As further required by the NJDEP, Defendant regularly sampled potable wells located on approximately forty residential properties in the vicinity of the Motiva site. Defendant detected small amounts of MTBE in thirteen of the residential wells it sampled.⁴

Per the NJDEP directive, Motiva submitted a Remedial Investigation Work Plan/Remedial Investigation report on July 2000 and a Remedial Action Workplan ("RAW") on November 14, 2000. In its RAW, Defendant requested permission to cease sampling of the residential wells, contending that the MTBE detected in those wells could not have come from the Motiva site since the wells are located upgradient⁵ or sidegradient from the site, and no emissions were detected in most of the monitoring wells between the Motiva site and the potable wells.⁶ Motiva also claimed that recent literature indicated that traces of MTBE in groundwater could likely result from "non-point sources." (March 2001 Directive at 2.)

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*2 Plaintiffs' expert, R. Brian Ellwood, Ph.D ("Ellwood"), submitted a response to the RAW on January 17, 2001. In his report, Ellwood notes that as of January 17, 2001, "[c]ontrol of contamination at depth beneath the site, control of offsite contamination, and possibly control of contamination at the northern site boundary, has not been established." (Preliminary Report Sicklerville Road Groundwater Contamination ("Ellwood Report"), McKenna Cert. in Opp. to Def.'s Mot. Summ. J., filed Oct. 12, 2005 ("McKenna Cert."), Ex. F, at 2.) Ellwood also offered possible theories to demonstrate the plausibility of Defendant's responsibility for the MTBE in spite of Motiva's arguments to the contrary.

The NJDEP ultimately rejected Defendant's request to cease sampling of the residential wells in its March 2001 Directive on the basis that "there is insufficient evidence for Equiva to conclude that the MTBE detected in the 13 potable wells in the area did not originate from the Cross Keys Texaco site" and "that regardless of the source of the MTBE in these wells, which is obviously debatable, ongoing sampling of these wells is required *primarily due to their proximity to the site.*" (March 2001 Directive at 2) (emphasis in original).

Also in the March 2001 Directive, the NJDEP approved a Classification Exemption Area ("CEA") for the site that excluded all but 1/10 of an acre of 583 Berlin Cross Keys Road (the Wallace Property). The CEA establishes the boundaries of a ground water plume where VOCs exceed the GWQS.⁷

Through summer 2004, the NJDEP regularly reduced the testing requirements. By August 18, 2003, the NJDEP required only:

annual sampling of the wells at 4, 7, 11, 13 and 14 Donna Marie Court; 2, 4, 6, and 8 Latham Way; 12 and 20 Spring Hollow Drive, and; 937 and 948 Sicklerville Road. For all the sampling events of the aforementioned potable wells conducted April 2002, the Department notes that all wells continue to exhibit no gasoline related contamination in

excess of the Department's Drinking Water Quality Standards.

(NJDEP Directive, Aug. 18, 2003, McKenna Cert., Ex. D.)

The NJDEP approved shut down of the recovery and treatment system on April 30, 2004. (NJDEP Correspondence, Aug. 9, 2004, Mairo Cert., Ex. S., at 2.) Finally, on August 9, 2004, the NJDEP determined that "Defendant's Remedial Action Progress Reports "meet the conditions of the March 21, 2001 Remedial Action Workplan (RAW) approval. Shell Oil Products U.S. (Shell OPUS) is, therefore, in compliance with N.J.A.C. 7:14B-6." (Aug. 9, 2004, NJDEP Correspondence, Mairo Cert., Ex. S., at 1.)

B. The Residential Properties

Plaintiffs own twenty-seven respective residential properties near Defendant's gasoline station.⁸ Twenty-six of the twenty-seven properties-all but 583 Berlin Cross Keys Road ("the Wallace property")-contain potable wells located in the Kirkwood Cohansey Aquifer. Because Plaintiffs' properties are north/northeast of the contamination site, (Undisputed Facts ¶ 38), they are considered upgradient or sidegradient of the contamination site, depending on whether CW-8 is pumping.⁹

*3 Consistent with the requirements of the NJDEP directives, Defendant tested the Plaintiffs' residential wells for six gasoline-related compounds: benzene, toluene, ethylbenzene, xylenes, MTBE, and TBA. No testing detected any gasoline-related compound on eighteen of the properties.¹⁰ Detection of compounds on the remaining eight properties was as follows:

- A single detection of 0.79 ppb toluene and ten detections of MTBE (highest at 15.5 ppb) at 4 Latham Way,
- Three detections of MTBE (highest at 0.76 ppb) at 14 Donna Marie Court,
- Three detections of MTBE (highest at 1.4 ppb) at 6 Latham Way,
- A single detection of 1.4 ppb toluene at 850 Sicklerville Road,

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- A single detection of 0.4 ppb MTBE at 4 Donna Marie Court,
- A single detection of 0.3 ppb MTBE at 12 Donna Marie Court,
- A single detection of 1.2 ppb MTBE at 8 Latham Way, and
- A single detection of 0.3 ppb MTBE at 20 Spring Hollow Road.

The GWQS for toluene is 1,000 ppb and the GWQS for MTBE is 70 ppb. No gasoline-related compound was detected on any Plaintiff's property after April 2001.

According to the Certification of Julian Davies, a Project Manager for EnviroTrac, Ltd., an environmental consulting firm retained by Defendant to remediate the Motiva site, the NJDEP never restricted the consumption of water from Plaintiffs' potable wells, and never required Defendant to treat the water, provide Plaintiffs with an alternate source of water, or collect soil samples from the residential properties.¹¹ (Julian Davies Cert., Mairo Cert., Ex. R, at 2.)

Since the fact of the contamination became known, several Plaintiffs have sold their property. Maria and John Wallace sold 583 Berlin Cross Keys Road for \$350,000.00 in September 2001, Plaintiffs Thomas and Tina Stankiewicz sold 9 Spring Hollow Drive in July 2002 for \$143,000.00, Barbara Tanner sold 17 Spring Hollow Drive for \$134,000.000 in February 2002, Daniel and Maria Rodriguez sold 18 Spring Hollow Drive for \$138,000.00 in July 2003, David Lodi sold 5 Donna Marie Court for \$104,000.00 in September 2001, 13 Donna Marie Court was sold for \$109,900.00 in July 2000, and 19 Spring Hollow Drive was sold for \$133,900.00 in May 2001.

Defendant filed motions for summary judgment and to exclude experts on June 24, 2005, after requesting and receiving permission from this Court to extend by one week the date for the filing of dispositive and *in limine* motions. Briefs in opposition were due July 22, 2005, however, Plaintiffs instead filed an untimely request for an extension on August 2, 2005, and a second request on September 6, 2005, moving the deadline to September 30, 2005. On October 5, 2005, Plaintiffs filed another untimely request for an extension, and ultimately did not submit a complete Opposition until October 14, 2005. Nevertheless, because a district court should not grant a

motion for summary judgment without examining the merits,

Stackhouse v. Mazurkiewicz, 951 F.2d 29, 30 (3d Cir.1991)

(citing *Anchorage Assoc. v. Virgin Islands Bd. of Tax Rev.*, 922 F.2d 168 (3d Cir.1990)), this Court will exercise its discretion to consider Plaintiffs' Opposition, even though it is untimely. Local Civ. R. 7.1(d)(5).

II. Standard

*4 Summary judgment is appropriate where the Court is satisfied that "there is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." Fed.R.Civ.P. 56(c); *Celotex Corp. v. Catrett*, 477 U.S. 317, 330, 106 S.Ct. 2548, 91 L.Ed.2d 265 (1986). A genuine issue of material fact exists only if "the evidence is such that a reasonable jury could find for the nonmoving party." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986).

The burden of establishing the nonexistence of a "genuine issue" is on the party moving for summary judgment.

Celotex, 477 U.S. at 330. The moving party may satisfy this burden by either (1) submitting affirmative evidence that negates an essential element of the nonmoving party's claim; or (2) demonstrating to the Court that the nonmoving party's evidence is insufficient to establish an essential element of the nonmoving party's case. *Id.* at 331.

Once the moving party satisfies this initial burden, the nonmoving party "must set forth specific facts showing that there is a genuine issue for trial." Fed.R.Civ.P. 56(e). To do so, the nonmoving party must "do more than simply show that there is some metaphysical doubt as to material facts." *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 586, 106 S.Ct. 1348, 89 L.Ed.2d 538 (1986). Rather, to survive summary judgment, the nonmoving party must "make a showing sufficient to establish the existence of [every] element essential to that party's case, and on which that party will bear the burden of proof at trial."

Serbin, 96 F.3d at 69 n. 2 (quoting *Celotex*, 477 U.S. at 322); *Heffron v. Adamar of N.J., Inc.*, 270 F.Supp.2d 562, 568–69 (D.N.J.2003). "If the non-movant's evidence on any essential element of the claims asserted is merely 'colorable' or is 'not significantly probative,' the court must enter summary judgment in favor of the moving party."

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Heffron, 270 F.Supp.2d at 69 (citing *Anderson*, 477 U.S. at 249–50).

III. Motion to Exclude Expert Daniel McDonald

Defendant moves to exclude the testimony of Plaintiffs' expert Daniel McDonald ("McDonald") on the grounds that he is unqualified and his report is unreliable.¹² Admissibility of expert testimony is governed by Federal Rule of Evidence 702 and the United States Supreme Court's decision in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993).¹³ In the Third Circuit, the admissibility of expert testimony is contingent on the "qualifications" of the expert and the "reliability" of his methodology. *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717 (3d Cir.1994) (interpreting *Daubert*); see also *Oddi v. Ford Motor Co.*, 234 F.3d 136, 145 (3d Cir.2000).

A. In Limine Hearing

In certain instances, courts are obligated to provide *in limine* hearings before applying *Daubert* to exclude expert testimony. *Padillas v. Stork-Gamco, Inc.*, 186 F.3d 412 (3d Cir.1999). A hearing is required, for example, where the court excludes an expert's conclusions on the grounds that they are "insufficiently explained and the reasons and foundations for them inadequately and perhaps confusingly explicated." *Id.* In other words, where a report is "conclusory and did not adequately explain the basis for [the expert's] opinion or the methodology employed in reaching his conclusions," the "plaintiff needs an 'opportunity to be heard' on the critical issues of scientific reliability and validity." *Oddi*, 234 F.3d 136, 152 (3d Cir.2000) (holding that the district court did not err "in granting summary judgment here without an *in limine* hearing") (quoting *Padillas*, 186 F.3d at 417). Where the evidentiary record is substantial, however, or the court has before it the information necessary to determine that the expert lacks "good grounds" for his conclusions, an *in limine* hearing may be unnecessary. *Id.* at 153.

*5 The evidence before this Court clearly establishes the process by which McDonald "arrived at his conclusions,"

Oddi, 234 F.3d at 152, and McDonald's report and deposition details the methodology underlying his determinations. As discussed below, this Court will exclude

McDonald's testimony on the grounds that his analysis and methodology are baseless and inconclusive, not because his report is insufficiently explained. Additionally, Defendant's motion for summary judgment alerted Plaintiffs to the *Daubert* challenge, yet Plaintiffs neither requested a hearing nor offered any affidavit or evidence in support of McDonald. Accordingly, an *in limine* hearing is unnecessary.

B. Qualifications

The Third Circuit instructs courts to "liberally" evaluate an expert's qualifications. *Oddi v. Ford Motor Co.*, 234 F.3d 136, 145 (3d Cir.2000). In particular, the Circuit has "eschewed overly rigorous requirements of expertise and [has] been satisfied with more generalized qualifications."

In re Paoli, 35 F.3d at 741 (citing *Hammond v. International Harvester Co.*, 691 F.2d 646, 652–53 (3d Cir.1982) and *Knight v. Otis Elevator Co.*, 596 F.2d 84, 87–88 (3d Cir.1979)). This liberal treatment extends to the expert's substantive qualifications as well as his formal qualifications. *Id.*

Nevertheless, the Third Circuit has "also set a floor with respect to an expert witness's qualifications." *Elcock v. Kmart Corp.*, 233 F.3d 734, 742 (3d Cir.2000). To demonstrate when an expert would not be qualified under Rule 702, the *Elcock* Court offered the pre-*Daubert* case, *Aloe Coal Co. v. Clark Equip. Co.*, 816 F.2d 110 (3d Cir.1987), which held a tractor salesperson unqualified to testify as an expert about the cause of a tractor fire. *Elcock*, 233 F.3d at 742 (citing *Aloe Coal*, 816 F.2d 110).

In *Elcock* itself, the Court determined with "misgivings" that the district court had not abused its discretion by concluding that a psychologist with experience in obtaining employment for disabled individuals was qualified to testify to the possibility for vocational rehabilitation of the injured plaintiff. However, the Court acknowledged that it also would have upheld a decision to exclude the expert since "he seems most qualified to testify on a micro-level regarding the ability of a disabled individual to return to a specific job; he does not appear particularly qualified to testify on the macro-level regarding the number of jobs in the national or local economy that the disabled individual is able to perform."¹⁴ *Elcock*, 233 F.3d at 744. Taken together, *Elcock* and *Aloe Coal* indicate that where a proposed expert's area of experience is

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adjacent to, but not actually encompassing, the subject matter of his testimony, he may be deemed unqualified.

McDonald has worked as a licensed appraiser in New Jersey for approximately twenty-two years. Defendant argues that McDonald is nevertheless unqualified to testify to the diminution in value of Plaintiffs' properties because McDonald has no experience in appraising contaminated property. Defendant notes that McDonald has never appraised property allegedly contaminated by emissions from a gasoline station and has never acted as an expert in a situation involving contamination of the groundwater or allegations of a leaking underground storage tank. (Daniel McDonald Dep. ("McDonald Dep."), Mairo Cert. in Supp. Def.'s Mot. to Exclude Plaintiffs' Expert Daniel McDonald, Ex. C, at 23–24.) Defendant also points out that McDonald did not entirely understand the Ellwood and Gallo reports upon which he relied, including the charts indicating the presence and degree of contaminating agents on the property. (McDonald Dep. at 55–56.)

*6 This case lies squarely between *Aloe Coal* and *Elcock*. Although McDonald is an experienced appraiser, no evidence indicates that he has any experience appraising contaminated properties or is qualified to value the effects of stigma on property values. Just as a psychologist experienced in assisting individuals to find work may be unqualified to testify about the general availability of jobs in the economy, an individual able to appraise an uncontaminated property may have no grounds for appreciating the devaluation of the same property under unique conditions of contamination or stigma. Because nothing in McDonald's experience indicates knowledge or expertise in issues of contamination, he is unqualified to testify to the loss of value to Plaintiffs' properties arising from the alleged contamination.

C. Reliability

Because expert testimony has the potential to bear considerable weight with a jury, the district court functions as a gatekeeper responsible for assuring "that the scientific methodology upon which the expert opinion is founded is reliable" and that "the expert's conclusion is based on good grounds." *In re Paoli*, 35 F.3d at 732–33. To ascertain "reliability," the court must examine a number of factors, both those established in *Daubert* and those previously enumerated by the Third Circuit in *United States v. Downing*, 753 F.2d

1224 (3d Cir.1985). *Oddi*, 234 F.3d 145 (citing *Paoli II*, 35 F.3d at 742). In particular, the court must consider:

- (1) whether a method consists of a testable hypothesis; (2) whether the method has been subjected to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non-judicial uses to which the method has been put.

Paoli II, 35 F.3d at 742 n. 8; *see also* *Elcock*, 233 F.3d at 746 (noting that "each factor need not be applied in every case"). The party wishing to introduce the testimony bears the burden of establishing "by a preponderance of the evidence that their opinions are reliable." *Paoli*, 35 F.3d at 744.

Of course, an expert's opinion need not be "perfect," and judges may not substitute their opinions for those of an expert. *Paoli*, 35 F.3d at 744; *see also* *Crowley v. Chait*, 322 F.Supp.2d 530, 536 (D.N.J.2004). However, courts also need not admit mere conclusions or "opinion evidence that is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered."

Magistrini v. One Hour Martinizing Dry Cleaning, 180 F.Supp.2d 584, 608 (D.N.J.2002) (quoting *General Elec. Co. v. Joiner*, 522 U.S. 136, 145–46, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997)).

*7 Mere assumptions, without causal evidence or methodological analysis may be inadmissible. *In re TMI Litig.*, 193 F.3d 613, 667–68 (3d Cir.1999). Conclusions based only on the expert's experience, *Oddi*, 234 F.3d at 140–41, and testimony founded on methods that are not

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generally accepted or lack testable hypotheses may also fail to surmount the *Daubert* standard, *Elcock*, 233 F.3d at 746. Furthermore, conclusions based on analogies that are too dissimilar to the subject of the testimony may also merit exclusion. *General Elec.*, 522 U.S. at 144 (rejecting expert testimony that plaintiff's cancer was due to exposure to PCBs when the testimony was based on animal studies of infant mice that had developed cancer after exposure to PCBs).

In response to Defendant's motion to exclude McDonald's testimony, Plaintiffs argue that "Mr. McDonald's opinions are based upon credible facts, NJDEP records, the reports of Plaintiffs' liability experts and individual appraisal reports prepared for each residential property." (Pls' Opp. Def.'s Mot. Summ. J. ("Opp."), filed Oct. 12, 2005, at 30.) However, McDonald testified in his deposition that he relied only on the Gallo and Ellwood Reports, and he specifically testifies that he did *not* "review any correspondence from the NJDEP related to this site." (McDonald Dep. at 15.)¹⁵

In spite of Plaintiffs' arguments to the contrary, this Court cannot avoid the conclusion that McDonald's methodology is entirely unreliable. In his report, McDonald determines that the value of Plaintiffs' properties with no evidence of contamination should be discounted 35% percent and property with onsite contamination should be discounted by 66%. (McDonald Report ("McDonald Report"), Mairo Cert. in Support of Def.'s Mot. Exclude Pls' Expert Daniel McDonald, Ex. B., at 31, 33.) McDonald reached the 35% and 66% figures without discussing, or even recognizing, the extent to which the property was actually contaminated. As demonstrated by his ignorance of the "ND"/Not Detected signifier in the Gallo and Ellwood Reports, McDonald did not know how to read the charts denoting the levels of contamination. (McDonald Dep. at 56.) Nor had McDonald ever conducted any physical inspection of or visit to the properties prior to writing the report.¹⁶ (McDonald Dep. at 15–16.)

Furthermore, to quantify the stigma attached to Plaintiffs' properties, McDonald relies upon a highly misleading analogy with a site of profoundly contaminated residential properties in Dover Township. (McDonald Report at 27.) Specifically, McDonald compares Plaintiffs' properties with "an area of Dover Township that had ground water contamination from Union Carbide and ... Ciba Geigy that resulted in what was commonly known as a cancer cluster among children," meaning "an inordinate number of children

with cancer." (McDonald Dep. at 158–59.) McDonald selected the Dover site not because of its comparability, but because McDonald "didn't know of any other cases that, where the data was as readily available." (McDonald Dep. at 159.)

*8 Employing the Dover analogy, McDonald determined that the property in the Dover site is in the final stages of recovery and continues to suffer a stigma loss of 13%. Because McDonald considered Plaintiffs' properties in the early stages of recovery, McDonald determined that they must bear a stigma discount of at least two or three times that of the Dover site, resulting in a discount of 35%.¹⁷ However, the severity of the contamination and resulting illness among Dover residents undercuts any grounds for comparison with Plaintiffs' properties where there were few detections of contaminants and no reported physiological effects.

The methodology employed to reach the 66% figure is equally unreliable. To assess the value of properties with some evidence of contamination, McDonald sent an email to thirteen financial lenders to determine whether they would "lend on a property that has known contamination, or the stigma of contamination, to the ground water." (McDonald Report at 32.) Of the thirteen lenders, six replied. One of those refused to comment, and one said that it would loan given certain circumstances. The other four lenders stated that they would not lend on a property that is contaminated, but the content of their brief responses suggested that they understood the email hypothetical to denote property that was actually contaminated and out of compliance with state requirements.¹⁸

From the results of the email test, McDonald concludes that there would be no buyers other than those who could pay cash.¹⁹ McDonald then assessed the discount in value given cash-only buyers, extrapolating from this a discount of 66%. (McDonald Report at 33.) However, the reliability of the 66% figure is entirely invalidated by the overemphasis placed on the four responses to the email hypothetical, the misleading implication in the email hypothetical, suggesting a much greater contamination of the property than actually present, and the unclear calculations and assumptions underlying McDonald's arrival at 66%.

Ultimately, McDonald's report does not fulfil any of the reliability factors. His method is untestable and arbitrary, without a generally accepted, established, or peer reviewed methodology, and his evaluation was conducted without any

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real standards. Because McDonald is unqualified and his evaluation is unreliable, Defendant's motion *in limine* to exclude his testimony will be granted.

IV. Plaintiffs' Claims

A. Negligence and Gross Negligence

To surmount a motion for summary judgment of a negligence claim, Plaintiffs must provide evidence such that a reasonable jury could find "breach of a duty of care and actual damages sustained as a proximate cause of the breach." *Muise v. GPU, Inc.*, 371 N.J.Super. 13, 35, 851 A.2d 799 (App.Div.2004) (citing *Weinberg v. Dinger*, 106 N.J. 469, 484, 524 A.2d 366 (1987)); *Nappe v. Anschelewitz, Barr, Ansell & Bonello*, 97 N.J. 37, 45, 477 A.2d 1224 (1984) ("[T]he plaintiff must show a breach of duty and resulting damage to prevail in a negligence action."). Motiva argues that Plaintiffs have failed to establish damages and causation and requests summary judgment of Plaintiffs' gross negligence claim on the same basis.²⁰

*9 The absence of an injury will preclude a negligence claim, even where a clear breach of duty is present. *Rocci v. MacDonald-Cartier*, 323 N.J.Super. 18, 24–25, 731 A.2d 1205 (App.Div.1999) (affirming summary judgment for insufficient evidence of damages in defamation case and noting that "a plaintiff must present proof of a material question of fact as to both liability and damages") (citing *Norwood Easthill Assoc. v. Norwood Easthill Watch*, 222 N.J.Super. 378, 384, 536 A.2d 1317 (App.Div.1988) (affirming summary judgment of malicious interference claim on basis that "plaintiff has suffered no injury or damage")). At the summary judgment stage, Plaintiffs must provide actual evidence of injury and cannot simply rely upon "unsubstantiated allegations." *Trap Rock Indus., Inc. v. Local 825*, 982 F.2d 884, 890 (3d Cir.1992) (reversing district court's denial of summary judgment). Just as "a residential customer not in residence during a power loss, or a commercial customer whose store was closed, might have no damages except the inconvenience of resetting clocks," *Muise*, 371 N.J.Super. at 49, 851 A.2d 799, the release of contaminants into the groundwater aquifer does not itself generate damages, unless Plaintiffs can show that they suffered harm.

Plaintiffs concede that they "have not presented and will not present claims for the present manifested bodily

injury." (Undisputed Facts ¶ 67.) However, they argue that they have adequately established damages for medical monitoring and property damage. They do not address their claim for emotional distress.²¹

1. Medical Monitoring

Damages for medical monitoring are appropriate where a plaintiff exhibits no physical injury, but nevertheless requires medical testing as a proximate result of a defendant's negligent conduct. *Ayers v. Jackson Twp.*, 106 N.J. 557, 600, 525 A.2d 287 (1987). The risk of injury need not be quantified to merit medical surveillance damages; however, the plaintiff must establish that the risk of serious disease is "significant." *Id.* at 599–600, 525 A.2d 287; *Campo v. Tama*, 133 N.J. 123, 131, 627 A.2d 135 (1993) (awarding medical monitoring damages to a plaintiff with a "fifty-to-seventy-five-percent chance of suffering a recurrence of cancer" due to the delay resulting from defendant doctor's malpractice). In the case of toxic exposure, "medical-surveillance damages may be awarded only if a plaintiff reasonably shows that medical surveillance is required because the exposure caused a distinctive increased risk of future injury." *Theer v. Philip Carey Co.*, 133 N.J. 610, 627, 628 A.2d 724 (1993). Such damages are "not available for plaintiffs who have not experienced direct and hence discrete exposure to a toxic substance and who have not suffered an injury or condition resulting from that exposure." *Id.* at 628, 628 A.2d 724.

Low level contamination, "that is, contamination below the minimum level set by DEP for water remediation," typically is insufficient to establish injurious toxic exposure.

Muralo Co., Inc. v. Employers Ins. of Wausau, 334 N.J.Super. 282, 290–291, 759 A.2d 348 (App.Div.2000) ("[S]ince it is clear that no untreated groundwater is ever entirely pure, we are satisfied that DEP standards are the most reliable guide for determining whether contamination causing damage ... has occurred."). Here, contaminants have been detected in only eight of Plaintiffs' wells, and no detection has been even close to the GWQS. The NJDEP never restricted Plaintiffs' use of water from their potable wells, nor required Defendant to treat Plaintiffs' wells or to provide Plaintiffs with an alternate water source.

*10 Plaintiffs rely on the testimony of Dr. Michael Gochfeld, Ph.D. ("Gochfeld"), to establish the significant health risks

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and necessity of medical surveillance following from the alleged contamination of Plaintiffs' property. However, nothing in Gochfeld's report concludes that the individual Plaintiffs themselves require medical monitoring under the circumstances. Rather, Gochfeld's report creates a medical monitoring program for a hypothetical target population without taking into consideration the actual exposure of any plaintiff.²² (Gochfeld Dep. at 26–29.) Gochfeld prepared his report under the assumption that “there were known or actual or potential exposure to a variety of constituents of gasoline.” (Gochfeld Dep. at 12.) He states in deposition that he had “no specific factual knowledge of the actual exposures in this case,” and he confirms that he has never examined the individual Plaintiffs. (Gochfeld Dep. at 10, 29.)

Gochfeld himself notes that “[w]hether a person exposed to MTBE requires medical monitoring depends in large measure on the level of exposure and the time over which it occurred” and notes that “clearly people that are exposed to MTBE casually would not require one.” (Gochfeld Dep. at 24.) Furthermore, Gochfeld stated that he “probably would not” recommend medical monitoring for the minor and often single detections of MTBE on Plaintiffs' properties.²³ (Gochfeld Dep. at 46–50.) Consequently, Gochfeld's report does not establish that Plaintiffs require medical monitoring.

Plaintiffs also appear to argue that their wells may have been more contaminated prior to the initiation of Defendant's testing in July 2000. (Opp. at 20.) However, Plaintiffs provide no evidence suggesting that such exposure actually occurred or that any exposure prior to July 2000 was more than minimal. Plaintiffs also argue for the first time in their Opposition that they may have ingested water from contaminated sources besides the potable wells on their property. (Opp. at 20.) However, Plaintiffs offer no evidence that any Plaintiff actually consumed water from CW–8. Without any evidence supporting their theories, Plaintiffs cannot establish a claim for medical monitoring sufficient to survive summary judgment.

Because Plaintiffs have provided no evidence of a “distinctive increased risk of future injury” from the exposure, Plaintiffs are not entitled to damages for medical monitoring.

2. Property Damage

Defendant requests summary judgment of Plaintiffs' claims of property damage on the grounds that the contamination caused no actual damage to Plaintiffs' properties.²⁴ Instead of

claiming that their property was physically harmed, Plaintiffs contend that the news of the contamination stigmatized their property, reducing its value in the minds of potential buyers.

In support of their claim for stigma damages, Plaintiffs offer the expert testimony of Daniel McDonald. However, as discussed previously, McDonald's testimony must be excluded as unreliable. Plaintiffs also argue that the testimony of individual Plaintiffs establishes a stigma discount to their property:

***11** Plaintiff Marie Wallace has submitted sworn Interrogatory statements documenting a \$150,000.00 loss on the sale of her property. See Exhibit O to McKenna Certification. Other Plaintiffs have similarly provided certified answers to Interrogatories and Deposition testimony as to the loss in value through sales transactions, which occurred from the discharge. See Exhibit N–R to the McKenna Certification.

(Opp. at 20–21.)

This evidence fails to establish an injury. Exhibits N–R consist of contracts for sale and unexecuted contracts for sale of three of Plaintiffs' properties, including the Wallace property, leaving it to the Court's imagination to ascertain how these contracts demonstrate a loss in value. Wallace's testimony also fails to establish a stigma injury to the property.

Specifically, Wallace claims that she received a verbal offer for her asking price of \$500,000.00 from a man named “Amin,” whose last name she cannot recall. (Marie Wallace Dep., McKenna Cert., Ex. O, M.) Wallace claims that he reneged from the agreement after she told him about the release, however, the alleged offeror never gave Wallace the offer in writing and she has no evidence of the offer or “Amin's” motive for withdrawing, aside from her own testimony. Consequently, even construing this evidence in the light most favorable to Plaintiffs, no reasonable jury could find that Plaintiffs' properties were stigmatized on the basis of this evidence alone.

3. Emotional Distress

Defendant also moves for summary judgment of Plaintiffs' claim for emotional distress. Plaintiffs do not respond to this argument in their Opposition, and Defendant is entitled to summary judgment of Plaintiffs' emotional distress claim for Plaintiffs' failure to present evidence of significant distress or physical injury.

A claim for emotional distress cannot succeed absent evidence of physical injury or "severe and substantial" emotional distress, even where a person has a reasonable concern of an enhanced risk of future disease. *Ironbound Health Rights Advisory Com'n v. Diamond Shamrock Chem. Co.*, 243 N.J.Super. 170, 174–75, 578 A.2d 1248 (App.Div.1990) (noting that "[i]n the absence of physical injury, damages are allowed where the resultant emotional distress is severe and substantial" and listing cases). Without some physical injury, mere exposure to toxic chemicals does not give rise to a claim for emotional distress damages. *Id.* (holding plaintiffs unable to sustain emotional distress claim for exposure to chemicals manufactured at plant near their residences); see also *Mauro v. Raymark Indus., Inc.*, 116 N.J. 126, 137, 561 A.2d 257 (1989); *Troum v. Newark Beth Israel Med. Ctr.*, 338 N.J.Super. 1, 17, 768 A.2d 177 (App.Div.2001). Because Plaintiffs provided no evidence of significant emotional distress or physical injury, Defendant's motion for summary judgment will be granted.

B. Trespass

Defendant moves for summary judgment of Plaintiffs' claim for trespass. Plaintiffs argue that Defendant's "intentional refusal" to remove the contamination from their property and failure to install remediation equipment amounts to an intentional trespass.²⁵ (Opp. at 25.)

*12 The Restatement (Second) of Torts defines intentional trespass as:

One who intentionally and without a consensual or other privilege

(a) enters land in possession of another or any part thereof or causes a thing or third person so to do, or

(b) remains thereon, or

(c) permits to remain thereon a thing which the actor or his predecessor in legal interest brought thereon in the manner

stated in §§ 160 and 161, is liable as a trespasser to the other irrespective of whether harm is thereby caused to any of his legally protected interests.

Rest. (2d) Torts § 158.

As Defendant argues, New Jersey has moved away from "such common law claims as trespass and nuisance" in environmental pollution cases. *Mayor and Council of Borough of Rockaway v. Klockner & Klockner*, 811 F.Supp. 1039, 1053 (D.N.J.1993); *Kenney v. Scientific, Inc.*, 204 N.J.Super. 228, 256, 497 A.2d 1310 (1985) ("There is no need for us ... to torture old remedies to fit factual patterns not contemplated when those remedies were fashioned."). Regardless of the continuing viability of trespass claims in the environmental context, however, Plaintiffs have failed to come forward with any evidence supporting their claim and cannot survive summary judgment.

Plaintiffs note that they are "not arguing that Defendants intentionally caused the contamination of their property," but rather are claiming that "defendants have repeatedly refused to perform the horizontal and vertical delineation of the soil and groundwater contamination in the area of the residential properties." (Opp. at 25.) However, no evidence suggests that such measures were necessary to remove contaminants from Plaintiffs' properties. Rather, the record indicates that Defendant consistently complied with NJDEP requirements, including the installation and maintenance of a groundwater recovery system to rehabilitate the aquifer, and the NJDEP never required Defendant to install any sort of remediation equipment on any of the residences. Given that there has been no detection of a gasoline-related contaminant in any Plaintiff's potable well since April 2001, the argument that Defendant permitted contamination to remain on Plaintiffs' properties lacks any viable evidentiary foundation. Defendant's motion for summary judgment of Plaintiffs' trespass claim will be granted.

C. Strict Liability

Plaintiffs originally claimed a cause of action for strict liability under the theory that the handling, storage, or use of gasoline constitutes an abnormally dangerous activity. However, Plaintiffs voluntarily dismissed this claim in their Opposition. (Pl.'s Opp. at 3.) Accordingly, the Court will not address the merits of Plaintiffs' strict liability claim.

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D. Environmental Statutes

1. New Jersey Environmental Rights Act

Plaintiffs allege a right to recover under the New Jersey Environmental Rights Act ("ERA"), N.J.S.A. 2A:35A-1 *et seq.* Defendant requests summary judgment on the grounds that Plaintiffs have not satisfied the ERA's notice provision, N.J.S.A. 2A:35A-11, and that an ERA claim is not actionable where the NJDEP has acted to institute and oversee remediation of the contamination.

*13 Section 4(a) of the ERA, permits "any person" to "maintain an action in a court of competent jurisdiction against any other person to enforce, or to restrain the violation of, any statute, regulation or ordinance which is designed to prevent or minimize pollution, impairment or destruction of the environment." N.J.S.A. 2A:35A-4(a). Although the ERA itself does not create substantive rights, it confers standing on private persons to enforce other environmental statutes, including the New Jersey Spill Compensation and Control Act ("Spill Act"). *Rockaway*, 811 F.Supp. at 1054; *Allied Corp. v. Frola*, 701 F.Supp. 1084, 1091 (D.N.J.1988).

The NJDEP is "entrusted initially with the right to determine the primary course of action to be taken." *Howell Township v. Waste Disposal, Inc.*, 207 N.J.Super. 80, 95, 504 A.2d 19 (App.Div.1986) ("In order to be effective, [the NJDEP] must normally be free to determine what solution will best resolve a problem on a state or regional basis given its expertise and ability to view those problems and solutions broadly."). Consequently, the right of private parties to sue under the EPA is "an alternative to inaction by the government which retains primary prosecutorial responsibility." *Superior Air Prod. Co. v. NL Indus., Inc.*, 216 N.J.Super. 46, 58, 522 A.2d 1025 (App.Div.1987); *Rockaway*, 811 F.Supp. at 1054 ("[T]he primary goal of the ERA is to limit lawsuits by private litigants to those instances where the government has not acted.").

A private ERA suit may be permitted even in the absence of complete government inaction if the NJDEP has "failed in its mission ... failed or neglected to act in the best interest of the citizenry or has arbitrarily, capriciously or unreasonably acted." *Howell*, 207 N.J.Super. at 96, 504 A.2d 19; *Morris County Transfer Station, Inc. v. Frank's Sanitation Serv., Inc.*, 260 N.J.Super. 570, 578, 617 A.2d 291 (App.Div.1992) (permitting private ERA

action where the NJDEP would not address violation for three years and had taken no enforcement actions against contaminating defendant who continued operating its illegal facility two months after receiving a violation notice). Where NJDEP "action subsequently proves sufficient to protect the environment," however, NJDEP "action under the Spill Act is preemptive of private rights under ERA." *Superior Air Prod.*, 216 N.J.Super. at 61, 522 A.2d 1025. The permissibility of private action must be evaluated on a case-by-case basis. *Id.*

Here the record indicates consistent and pervasive NJDEP oversight of the remediation process, requiring Defendant to regularly test Plaintiffs' wells and institute interim and permanent groundwater recovery systems. Plaintiffs have not claimed that the NJDEP failed to act or acted unreasonably, and there are no grounds for finding NJDEP inaction sufficient to permit a private ERA suit. Furthermore, as discussed below, Plaintiffs failed to give the NJDEP the requisite notice of their private suit. Accordingly, Defendant's motion for summary judgment of Plaintiffs' ERA claim will be granted.

2. Notice

*14 Before a private party may commence an action under the ERA, the party must "at least 30 days prior to the commencement thereof, direct a written notice of such intention by certified mail, to the Attorney General, the Department of Environmental Protection, the governing body of the municipality in which the alleged conduct has, or is likely to occur, and to the intended defendant." N.J.S.A. 2A:35A-11. The notice provision is intended to give the government an adequate opportunity to intervene in the litigation and to allow the NJDEP:

to exercise value judgments in individual cases, e.g., whether it will join in that litigation or enforcement proceeding, whether other actions it may have taken already with respect to the particular problem or offender would render the litigation subject to collateral estoppel or res judicata principles, whether its expertise would assist the court, whether broad State interests would be sacrificed unduly to

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regional or personal interests by the instigators of that litigation, etc.

Howell, 504 A.2d at 95; *Morris County*, 260 N.J.Super. at 578, 617 A.2d 291 (quoting *Howell* for same).

Because Plaintiffs did not provide the required thirty day notice to the NJDEP or the Attorney General, they are barred from further pursuing their claim under the ERA. Plaintiffs argue that Defendant is judicially estopped from claiming lack of notice for failure to raise this issue at an earlier stage in the case. Plaintiffs analogize the ERA requirement to that of an affidavit of merit, required in certain cases to avoid “unmeritorious and frivolous malpractice lawsuits at an early stage of litigation.” *Knorr v. Smeal*, 178 N.J. 169, 197–98, 836 A.2d 794 (2003) (holding judicially estopped defendant's request for summary judgment for plaintiff's failure to file affidavit of merit) (citing *Palanque v. Lambert–Woolley*, 168 N.J. 398, 404, 774 A.2d 501, 505 (2001)); *Ferreira v. Rancocas Orthopedic Assoc.*, 178 N.J. 144, 836 A.2d 779, (2003) (same).

Defendant argues that the ERA notice requirement is more analogous to the notice of intent in the Resource Conservation and Recovery Act (RCRA), which the Supreme Court held to be a jurisdictional prerequisite to suit in *Hallstrom v. Tillamook County*, 493 U.S. 20, 31, 110 S.Ct. 304, 107 L.Ed.2d 237 (1989) (“[C]ompliance with the 60–day notice provision is a mandatory, not optional, condition precedent for suit.”); *Public Interest Research Group of N.J., Inc. v. Windall*, 51 F.3d 1179, 1189 (3d Cir.1995) (holding notice provision jurisdictional in context of Clean Water Act (“CWA”)); *Hawksbill Sea Turtle v. Federal Emergency Mgmt. Agency*, 126 F.3d 461, 471 (3d Cir.1997) (holding notice provision jurisdictional in context of Endangered Species Act (“ESA”)).

However, the language of the notice requirement in RCRA is not entirely analogous to that of the ERA. RCRA states, under the heading of “Actions prohibited” that “No action may be commenced ... prior to 60 days after the plaintiff has given notice of the violation to” the Administrator, the state and the alleged violator. 42 U.S.C.A. § 6972. The ERA lacks the “no action may be commenced” language of the RCRA, CWA, and ESA, and states only that notice must be sent “at least

30 days prior to the commencement” of suit. Consequently, the argument that the plain language of the statute creates a jurisdictional bar is not as strong in the context of the ERA.

*15 Nevertheless, because the purpose of the notice provision is to provide the Attorney General and NJDEP with notice of the suit and opportunity to intervene, *Howell*, 504 A.2d at 95, and not merely to protect defendants, as in the case of the affidavit of merit, Defendant is not judicially estopped from raising Plaintiffs' lack of compliance with the notice provision and is entitled to summary judgment of Plaintiffs' ERA claim.

E. Spill Act Claim

In their complaint, Plaintiffs assert a private right of action under the Spill Act, N.J.S.A. 58:10–23.11 *et seq.*²⁶ As amended in 1991, the Spill Act authorizes a private cause of action for individuals to recover costs for environmental damage to their property. *Housing Auth. of City of New Brunswick v. Suydam Inv., L.L.C.*, 177 N.J. 2, 18, 826 A.2d 673 (2003). Actions under the Spill Act are limited to clean up and removal costs, *Bahrle v. Exxon Corp.*, 145 N.J. 144, 155, 678 A.2d 225 (1996), defined as:

all direct costs associated with a discharge, and those indirect costs that may be imposed by the department pursuant to section 1 of P.L.2002, c. 37 associated with a discharge, incurred by the State or its political subdivisions or their agents or any person with written approval from the department in the: (1) removal or attempted removal of hazardous substances, or (2) taking of reasonable measures to prevent or mitigate damage to the public health, safety, or welfare, including, but not limited to, public and private property.

N.J.S.A. 58:10–23.11b(d). The Act does not authorize “damages arising from emotional distress, enhanced risk of disease, loss of enjoyment of property, and other economic and financial harm.” *Bahrle*, 145 N.J. at 155, 678 A.2d 225. Plaintiffs maintain that the investigation conducted by Ellwood was a reimbursable clean up and removal cost under the Spill Act. As Plaintiffs suggest, because “a discharge cannot be addressed until the contaminants are defined and the extent of the discharge determined,” certain forms of investigative costs are implicitly included in the Act.

Metex Corp. v. Federal Ins. Co., 290 N.J.Super. 95, 115, 675 A.2d 220 (App.Div.1996).

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However, for a private party to obtain reimbursement under the Act, the party must have obtained "written approval from the department," for example, in a memorandum of agreement, prior to incurring the cost. N.J.S.A. 58:10–23.11b(d); *Id.* Such approval permits the NJDEP to "review and approve or disapprove its investigation to date, its proposed remedial action, and its report of the implementation of its action." *Id.*; see also *Interfaith Cmty Org. v. Honeywell Intern., Inc.*, 263 F.Supp.2d 796, 867 (D.N.J.2003) (concluding "that such costs were approved by and/or incurred at the direction of NJDEP and thus are recoverable

under the Spill Act.""). Because Plaintiffs have not obtained NJDEP approval for any cost incurred, including the Ellwood report, Defendant is entitled to summary judgment of Plaintiffs' Spill Act Claim.

*16 The accompanying Order shall enter today.

Elcock, 233 F.3d at 741.

All Citations

Not Reported in F.Supp.2d, 2006 WL 166452

Footnotes

- 1 The following facts are taken from Defendant's statement of undisputed material facts, filed June 24, 2005, ("Undisputed Facts") and Plaintiffs' counterstatement of undisputed facts, filed Oct. 14, 2005, ("Counterstatement Facts"). Plaintiffs did not provide a separate statement of undisputed facts. Although Plaintiffs dispute the majority of Defendant's statements of fact, Plaintiffs' counterstatements typically provide additional facts without setting forth any conflicting evidence. Where no actual disputes are presented, Defendant's statements will be treated as undisputed. See e.g., *Tofano v. Reidel*, 61 F.Supp.2d 289, 292 n. 1 (D.N.J.1999) (citing Fed.R.Civ.P. 56(e)) ("This court will ... not consider assertions without evidential support as creating genuine issues of disputed fact."); *Talbot v. United States*, 2005 WL 2917463, *2 (D.N.J.2005) (noting that where the nonmoving party does not submit facts in opposition, "it is entirely appropriate for this court to treat all facts properly supported by the movant to be uncontroverted") (quoting *Allebach v. Sherrer*, No. 04–287, 2005 U.S. Dist. LEXIS 15626, at *5 (D.N.J.2005)). More generally, Plaintiffs' brief suffers from numerous typographical errors and a dearth of citations to page numbers in the record. This "alone warrants exclusion of the evidence." See *Orr v. Bank of America, NT & SA*, 285 F.3d 764, 774–75 (9th Cir.2002) (holding that party's failure to cite page and line numbers when referencing the deposition merits exclusion of evidence); *Huey v. UPS, Inc.*, 165 F.3d 1084, 1085 (7th Cir.1999) ("[J]udges need not paw over the files without assistance from the parties."); *Nissho-Iwai Am. Corp. v. Kline*, 845 F.2d 1300, 1307 (5th Cir.1988) (parties must designate specific facts and their location in the record).
- 2 Among the original litigants to the suit were also former plaintiffs Michael and Susan Kammerhoff and Norma Simmons. The Kammerhoff plaintiffs were voluntarily dismissed, and plaintiff Norma Simmons died on August 26, 2000.
- 3 VOCs generally associated with gasoline discharge include MTBE, benzene, toluene, ethylbenzene, xylene (collectively "BTEX"), and tertiary butyl alcohol ("TBA"). The NJDEP has issued a Ground Water Quality Standard ("GWQS") for each of these VOCs, also known as "gasoline-related compounds." MTBE, for example, has a GWQS of 70 parts per billion ("ppb").
- 4 Although Motiva detected MTBE in thirteen residential wells, not all of these wells are owned by Plaintiffs to this litigation. Of the twenty-seven parcels of property at issue in this suit, only eight of the properties contain wells that ever tested positive for any gasoline-related compound.
- 5 The direction of water's flow in an aquifer is described as "downgradient," and the direction against the current is "upgradient."

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- 6 In particular, testing revealed emissions in monitoring wells 6–Shallow (“MW–6S”) and 7–Deep (“MW–7D”), which lie between the Motiva site and the residential properties. However, the majority of upgradient monitoring wells did not test positive for gasoline-related contaminants. (NJDEP Directive, March 21, 2001 (“March 2001 Directive”), Mairo Cert. in Supp. Def.’s Mot. Summ. J., filed June 24, 2005 (“Mairo Cert.”), Ex. O, at 4.)
- 7 Plaintiffs dispute Defendant’s characterization of the CEA, (Counterstatement Facts ¶¶ 31), on the basis that Defendant proposed the CEA prior to conducting an actual delineation of the plume and that “the Plaintiffs’ residential wells could only had [sic] been included in the CEA, if Defendant intended to supply a permanent public water supply to Plaintiffs’ properties.” While Plaintiffs’ contention with the CEA is not entirely clear, Plaintiffs have not provided any evidence indicating that the NJDEP improperly approved the CEA or that the CEA was an inaccurate representation of the boundaries of contaminants in excess of the GWQS.
- 8 Plaintiffs’ properties are: 850 Sicklerville Road; 565, 569, 581, and 583 Berlin–Cross Keys Road; 6, 9, 10, 12, 13, 14, 1, 16, 17, 18, 20 Spring Hollow; 2, 4, 6, and 8 Latham Way; 3, 4, 5, 7, 12, 14, and 15 Donna Marie Court.
- 9 CW–8 is located approximately 1,000 feet downgradient of the contamination site. (March 2001 Directive at 2.) While active, CW–8 pumps approximately 500 gallons per minute and causes the groundwater to flow southwest. (Ellwood Report at 2.) When CW–8 is not pumping, the groundwater flow is more westerly. (Ellwood Report at 2.)
- 10 Plaintiff disputes these facts on the basis that:
- The Defendant has no data for any portable [sic] water supply of the Plaintiffs prior to July 2000. The Defendant never performed any delineation of the groundwater plume in the areas of the residential properties despite having actual knowledge of such contamination in MW–6, MW–7 and MW–12. See Gallo Certification and Exhibits C, D and E.
- (Counterstatement Facts ¶¶ 46–48.) However, because Defendant makes no averment of the presence or absence of contamination prior to July 2000, Defendant’s statements are not actually in dispute. Plaintiffs provide no fact indicating an inaccuracy in Defendant’s statements regarding the testing of Plaintiffs’ wells. Consequently, there is no actual dispute regarding the presence or amount of *detected* gasoline-related compounds.
- 11 Plaintiffs dispute these statements by citing to Exhibit F of the McKenna certification; however, Exhibit F is the Ellwood report and therefore is not indicative of the NJDEP requirements. Plaintiffs nowhere cite to a statement by the NJDEP requiring Defendant to treat their water or provide them with an alternate water source, and therefore this fact is undisputed.
- 12 Because this Court will grant Defendant’s motion for summary judgment, it will not reach the merits of Defendant’s motions to exclude experts Gochfeld, Ellwood, and Gallo.
- 13 After *Daubert*, Rule 702 was amended to encompass the *Daubert* analysis:
- If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.
- Fed.R.Evid. 702. While *Daubert* itself addressed only the admissibility of scientific evidence, the Court has since noted that courts’ gatekeeping obligations extend to all expert testimony. *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 151, 119 S.Ct. 1167, 143 L.Ed.2d 238 (1999).
- 14 The Court noted that it had “misgivings” about the expert’s qualifications in spite of:
- (1) [the expert’s] general training in “assessing” individuals, which he received while earning his Ph.D. in psychology; (2) his experience, twenty years previous, helping drug addicts reenter the workforce; (3) his experience primarily in the last two years dealing with the Virgin Islands Division of Workers’ Compensation, which he had advised regarding the ability of approximately fifty to sixty-five disabled employees to return to their previous jobs; (4) his past experience as an expert witness making lost earning capacity assessments;

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(5) his attendance at two seminars regarding vocational rehabilitation, and his stated familiarity with the literature in the area; (6) his membership in two vocational rehabilitation organizations, both of which place no restrictions on membership; and (7) the fact that when [the expert] was in school, a degree in vocational rehabilitation therapy was not available, but that he received similar training nonetheless.

15 Plaintiffs also argue that "Defendant does not attack the methodology, standard or factual basis for the opinions," (Opp. at 31), however, it is quite clear from Defendant's motion that the reliability of McDonald's methodology is hotly disputed.

16 McDonald also appeared unaware of the fact that Plaintiffs' properties are served by potable wells, even though the potable wells contain the evidence of contamination.

Q: Do you know whether or not the plaintiffs' properties have potable wells?

A: It's my understanding that they are hooked to a public water system.

Q: If each of the properties did in fact have a potable well, would that be a factor that you were consider relevant in your analysis?

Mr. McKenna: You may want to review the documents that you referenced in your report to assist you in this area. Just separate the Ellwood and Gallo reports. I'm going to go to the men's room.

(Whereupon, a recess is taken.)

Mr. Mairo: I am going to object that Mr. McKenna was basically coaching the witness.

Back on the record.

A: Your question about whether or not each of these houses were, was, had their own private well on site-

Q: Uh-huh?

A: -it's my understanding that each house is served by wells within and around the neighborhood and that Consumer, Consumers Water Company owns those wells and supplies that water to the homes.

(McDonald Dep. at 36.)

17 McDonald reaches the 35% devaluation figure with the following methodology:

The subject properties are in the early stages of monitoring, and clean up of the ground water contamination. The properties from Dover Twp. are beyond the clean up stage and into the final stage of recovery, yet they still show a 13% loss in value as compared to similar properties outside of the contaminated area. The subject area is in stage D of recovery, which is the beginning of the remediation process. Based on the acceptance of the Detrimental Condition Model as a viable process for valuing Detrimental Conditions to Real Estate, by the appraisal community and the Subcommittee on Housing and Community Opportunity of the House Committee on Financial Services, it would be logical to assume that the discount to the properties which are the subject of this report, would be 2 to 3 times that of properties in the final stage of recovery. In this case a discount of 35% would be considered reasonable.

(McDonald Report at 31.)

18 Interbay Funding, for example, qualified their statement that they would not lend by noting, "The property would have to be completely cleaned up. They would have to file all necessary documents to the state of NJ and we would require something from the state telling us the property is cleaned up." (McDonald Report at 32.) From this, McDonald concluded that Interbay Funding would not lend on properties such as Plaintiffs', without considering that none of Plaintiffs' properties were contaminated in excess of state standards.

19 In evaluating this data, McDonald states:

The lenders that did respond have overwhelmingly stated that they would not approve the loan at all, or they would require substantial conditions to the loan. In the case of the subject properties, it can be assumed that a purchaser with private financing or cash would be the only potential buyer of houses in this area.

(McDonald Report at 32.)

20 Because the Court now finds that there is no evidence of any actual injury arising from Defendant's negligence, this Court will not address Defendant's causation argument.

21 Plaintiff argues that Defendant's motion for summary judgment of its negligence claim should be denied on the basis of the doctrine of *res ipsa loquitur*. However, *res ipsa loquitur* acts only to "permit[] an inference of defendant's negligence" (i.e., that defendant acted in an unreasonable manner) under particular

circumstances. *Jerista v. Murray*, 185 N.J. 175, 192, 883 A.2d 350 (2005). The doctrine does not establish either causation or the presence of damages. See e.g., *Bahrle v. Exxon Corp.*, 279 N.J. Super. 5, 35, 652 A.2d 178 (App.Div.1995) (holding *res ipsa* doctrine inapplicable where "there was a factual dispute as to whether the contamination was a result of plaintiffs' own voluntary acts or neglect"). Accordingly, because Defendant is contesting only causation and damages, the *res ipsa* doctrine does not apply.

22 Gochfeld testifies in his deposition that he created his report without any specific information about the Plaintiffs:

Q: So, for example, in determining the percentage of the target population that was in high exposure category, that wasn't based on the ground water, your review of the ground water tables that were attached to Mr. Gallo's report?

A: It was not.

Q: That was based purely on just an assumption of yours?

A: It was an assumption based on experience with previous programs or programs that are currently underway in our communities.

Q: Having no specific factual knowledge of the actual exposures in this case?

A: That's correct, these are hypotheticals.

(Gochfeld Dep. at 28–29.)

23 Gochfeld also states that he would not even recommend medical monitoring for the one property with by far the highest detection of MTBE (13.8 ppb at 4 Latham Way) "on this data alone" because "[i]t is possible that a person living there would only be drinking bottled water, would not be in the house very much." (Gochfeld Dep. at 50.)

24 Defendant argues further that New Jersey law does not permit Plaintiffs to recover for stigma damages in the absence of some physical harm to their property. Because Plaintiffs have provided no evidence of any stigma to their property, the Court will not reach Defendant's alternative argument.

25 It is unclear whether Plaintiffs allege negligent trespass since they discuss only the Restatement (Second) of Torts § 158, Intentional Trespass, in their Opposition. Unlike intentional trespass, negligent or reckless trespass requires evidence of "harm to the land, to the possessor, or to a thing or a third person." Rest.

Torts 2d § 165; see also *Burke v. Briggs*, 239 N.J. Super. 269, 271, 571 A.2d 296 (App.Div.1990) (citing Rest.2d Torts § 158 with approval for another premise); *Karpjak v. Russo*, 450 Pa. Super. 471, 481, 676 A.2d 270 (Pa. Super.1996) (affirming dismissal of trespass claim for entry of dust onto property since the "evidence failed to establish that the dust caused appellants harm"). As discussed previously, Plaintiffs have not provided any evidence of injury to their persons or property. Consequently, to the extent that Plaintiffs are claiming negligent trespass, Defendant is entitled to summary judgment.

26 It is unclear whether Plaintiffs also raise a claim for cleanup and removal costs from the Spill Compensation

Fund under N.J.S.A. 58:10–23.11g(a). (Opp. at 12–13.) However, the appropriate procedure to obtain compensation under the Fund is by filing a claim with the administrator of the Fund, "not later than one year after the date of discovery of damage. The administrator shall prescribe appropriate forms and procedures for such claims." N.J.S.A. 58:10–23.11k. In the event "a party, including a potentially responsible party ... contests the amount or validity of" a claim for reimbursement from the Spill Fund, "the dispute is referred to an arbitrator whose decision may be appealed to the Appellate Division," and the arbitrator's decision will be final unless it was "arbitrary, capricious, or unreasonable." *Lacey Municipal Util. Auth. v. New Jersey Dept. of Envir. Prot., Envir. Claims Admin.*, 369 N.J. Super. 261, 273, 848 A.2d 843 (App.Div.2004). Accordingly, this is an improper forum for a Spill Compensation Fund claim.

Exhibit P

FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan)

Get updates on the recalls

Update: 11/13/2019 - FDA warns Mylan for CGMP deviations

Update [11/13/2019] Today, the U.S. Food and Drug Administration posted a warning letter ([/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/mylan-laboratories-limited-unit-8-589297-11052019](https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/mylan-laboratories-limited-unit-8-589297-11052019)) to Mylan Pharmaceuticals, Inc. in Chodavaram Village, Vizianagaram, Andhra Pradesh, India. Mylan manufactures valsartan active pharmaceutical ingredient (API) and has been one subject of an ongoing global investigation into nitrosamine impurities in angiotensin II receptor blockers (ARBs) such as valsartan, losartan and irbesartan.

The warning letter outlines several current good manufacturing practice (CGMP) deviations at this Mylan facility, including failure to have adequate written procedures for the receipt, identification and handling of raw materials and failure to adequately clean equipment and utensils. Failure to correct these deviations may result in further action by the agency. The warning letter is another result of the agency's ongoing investigation.

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

Update: 10/15/2019 - FDA warns Torrent for CGMP violations

Update [10/15/2019] Today, the U.S. Food and Drug Administration posted a warning letter ([/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/torrent-pharmaceuticals-limited-585255-10082019](https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/torrent-pharmaceuticals-limited-585255-10082019)) to Torrent Pharmaceuticals in Ahmedabad, Gujarat, India. Torrent manufactures losartan potassium tablets and has been one subject of an ongoing global investigation into nitrosamine impurities in angiotensin II receptor blockers (ARBs) such as valsartan, losartan and irbesartan.

The warning letter outlines several manufacturing violations at Torrent's Taluka-Kadi, Indrad, Gujarat facility, including failure to follow written procedures for production and process control and failure to adequately investigate batch discrepancies. Failure to correct

these violations may result in further action by the agency. The warning letter is another result of the agency's ongoing investigation.

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

Update: 9/20/2019 - Torrent expands its voluntary recall of losartan

Update [9/20/2019] Torrent Pharmaceuticals is expanding its voluntary [recall \(/safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-expands-voluntary-nationwide-recall-losartan-potassium-o\)](#) to include five additional lots of losartan potassium tablets (three lots of losartan potassium tablets and two lots of losartan potassium/hydrochlorothiazide (HCTZ) combination tablets). This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient manufactured by Hetero Labs Limited. Torrent is recalling lots of losartan-containing medication that tested positive for NMBA above 9.82 parts per million.

The agency updated the list of [recalled angiotensin II receptor blockers \(ARBs\) \(/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and\)](#) accordingly.

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

8/28/2019: STATEMENT: Statement on the agency's ongoing efforts to resolve safety issue with ARB medications

Go to [FDA Statement \(/news-events/press-announcements/statement-agencys-ongoing-efforts-resolve-safety-issue-arb-medications\)](#).

6/26/2019: UPDATE - Macleods Pharmaceuticals voluntarily recalls losartan containing NMBA

Update [6/26/2019] FDA is alerting patients and health care professionals to Macleods Pharmaceuticals' voluntary [recall \(/safety/recalls-market-withdrawals-safety-alerts/macleods-pharmaceutical-limited-issues-voluntary-nationwide-consumer-level-recall-losartan-potassium\)](#) of two lots of losartan potassium tablets (50mg strength) and 30 lots of losartan potassium/hydrochlorothiazide (HCTZ) combination tablets (12 lots of

50mg/12.5mg strength, three lots of 100mg/12.5mg strength, and 15 lots of 100mg/25mg strength). This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited.

FDA is working with manufacturers to reduce and remove nitrosamines from angiotensin II receptor blockers (ARBs). The agency also updated the list of [recalled angiotensin II receptor blockers \(ARBs\) \(/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and\)](#).

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

6/12/2019: UPDATE - Teva expands its voluntary recall of losartan

Update [6/12/2019] Teva Pharmaceuticals is expanding its voluntary [recall \(/safety/recalls-market-withdrawals-safety-alerts/teva-pharmaceuticals-usa-inc-expands-voluntary-nationwide-recall-losartan-potassium-50-mg-and-100-mg\)](#) to include seven additional lots of losartan potassium tablets (three lots of 50 mg strength and four lots of 100 mg strength) labeled by Golden State Medical Supply. This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited. Teva is recalling lots of losartan-containing medication that tested positive for NMBA above 9.82 parts per million.

The agency updated the list of [recalled angiotensin II receptor blockers \(ARBs\) \(/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and\)](#) accordingly.

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

5/6/2019: UPDATE - FDA alerts patients and health care professionals to Vivimed's recall of losartan medication due to NMBA

Update [5/6/2019] FDA is alerting patients and health care professionals to a voluntary [recall \(/safety/recalls-market-withdrawals-safety-alerts/vivimed-life-sciences-pvt-ltd-issues-voluntary-nationwide-recall-losartan-potassium-25-mg-50-mg-and\)](#) of 19 lots of

losartan potassium tablets made by Vivimed Life Sciences Pvt Ltd in Alathur, Chennai, India and distributed by Heritage Pharmaceuticals Inc, East Brunswick, New Jersey, due to the detection of the impurity N-Nitroso-N-methyl-4-aminobutyric acid (NMBA). Vivimed is recalling lots of losartan-containing medication that tested positive for NMBA above 9.82 parts per million.

Manufacturers should contact FDA's Drug Shortages Staff when their testing of losartan shows levels of NMBA that exceed the interim acceptable intake limit (<https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan#interimlimits2>) of 0.96 ppm. FDA will determine, on a case-by-case basis, whether lots containing NMBA greater than 0.96 ppm should be released for distribution.

FDA reminds patients taking recalled angiotensin II receptor blockers (ARBs) to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

The agency also updated the list of recalled ARBs ([/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and](https://www.fda.gov/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and)).

5/2/2019: UPDATE - Laboratory analysis of valsartan products

Update [5/2/2019] FDA posted laboratory test results showing NDEA levels in recalled valsartan products ([/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products](https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products)) as well as an assessment of the cancer risk from NDEA in valsartan.

4/29/2019: UPDATE - FDA alerts patients and health care professionals to Teva's recall and Legacy's expanded recall of losartan medication due to NMBA

Update [4/29/2019] FDA is alerting patients and health care professionals to a voluntary recall ([/safety/recalls-market-withdrawals-safety-alerts/teva-pharmaceuticals-usa-inc-issues-voluntary-nationwide-recall-losartan-potassium-25-mg-and-100-mg](https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/teva-pharmaceuticals-usa-inc-issues-voluntary-nationwide-recall-losartan-potassium-25-mg-and-100-mg)) of 44 lots of losartan potassium tablets manufactured by Teva Pharmaceuticals and labeled as Golden State Medical Supply due to the detection of the impurity N-Nitroso-N-methyl-4-aminobutyric acid (NMBA). The recalled products were made with active pharmaceutical ingredient (API) manufactured by Hetero Labs. Teva is recalling lots of losartan-containing medication that tested positive for NMBA above 9.82 parts per million. Additionally, Legacy expanded its recall ([/safety/recalls-market-withdrawals-safety-alerts/legacy-pharmaceutical-packaging-llc-expands-voluntary-nationwide-recall-losartan-potassium-tablets](https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/legacy-pharmaceutical-packaging-llc-expands-voluntary-nationwide-recall-losartan-potassium-tablets)) to include one additional lot of losartan tablets made with API

manufactured by Hetero Labs.

Manufacturers should contact FDA's Drug Shortages Staff when their testing of losartan shows levels of NMBA that exceed the interim acceptable intake limit of 0.96 ppm. FDA will determine, on a case-by-case basis, whether lots containing NMBA greater than 0.96 ppm should be released for distribution.

The agency also updated the list of [recalled losartan medicines \(/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and\)](/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and).

4/19/2019: UPDATE - Torrent further expands its voluntary recall of losartan; FDA posts new nitrosamine testing methods

Update [4/19/2019] Torrent Pharmaceuticals Limited is further expanding its voluntary recall (</safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-expands-voluntary-nationwide-recall-losartan-potassium>) to include 104 additional lots of losartan potassium and losartan potassium/hydrochlorothiazide combination tablets. This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited.

The agency updated the list of [losartan products under recall \(/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and\)](/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and) accordingly.

FDA reminds patients taking recalled angiotensin II receptor blockers (ARBs) to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

FDA is also posting new testing methods which can help manufacturers and international regulators detect and identify multiple nitrosamine impurities. FDA and international regulators have identified N-Nitrosodimethylamine (NDMA), N-Nitrosodiethylamine (NDEA) and NMBA in ARBs.

- A [direct injection GC-MS method \(/media/123409/download\)](/media/123409/download) that is able to detect NDMA, NDEA, N-Nitrosodiisopropylamine (NDIPA), N-Nitrosoethylisopropylamine (NEIPA), and N-nitrosodibutylamine (NDBA)
- A [headspace GC-MS method \(/media/124025/download\)](/media/124025/download) that is able to detect NDMA, NDEA, NDIPA, and NEIPA

These methods should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

4/4/2019: STATEMENT - Statement from FDA Commissioner Scott Gottlieb, M.D., and Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research on the agency's list of known nitrosamine-free valsartan and ARB class medicines, as part of agency's ongoing efforts to resolve ongoing safety issue

Go to [FDA Statement \(/news-events/press-announcements/fda-statement-agencys-list-known-nitrosamine-free-valsartan-and-arb-class-medicines-part-agencys\)](/news-events/press-announcements/fda-statement-agencys-list-known-nitrosamine-free-valsartan-and-arb-class-medicines-part-agencys).

3/22/2019: UPDATE - FDA updates recalled valsartan-containing and losartan-containing medicine information

Update [3/22/2019] FDA has updated the [list of valsartan medicines under recall \(/media/118231/download\)](/media/118231/download) to incorporate additional repackagers of Aurobindo's valsartan-containing medicine. FDA has also updated the [list of losartan medicines under recall \(/media/119422/download\)](/media/119422/download) to include repackagers of Torrent's and Camber's losartan-containing medicines.

The agency also updated the [list of valsartan medicines not under recall \(/media/118232/download\)](/media/118232/download) accordingly.

3/20/2019: UPDATE - FDA not objecting to losartan with NMBA below 9.82 ppm remaining on the market

Update [3/20/2019] To ensure patient access to losartan, FDA will not object to certain manufacturers temporarily distributing losartan containing N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) above the [interim acceptable intake limit](#) of 0.96 parts per million (ppm) and below 9.82 ppm until the impurity can be eliminated. The agency expects many companies will be able to manufacture losartan without nitrosamine impurities and replenish the U.S. supply in approximately six months.

Agency scientists evaluated the risk of exposure to NMBA at levels up to 9.82 ppm and determined that it presents no meaningful difference in cancer risk over a six-month time period when compared to a lifetime of exposure to NMBA at 0.96 ppm. Distributing losartan containing NMBA up to 9.82 ppm, will help maintain adequate losartan supply while companies obtain approval for manufacturing processes that produce nitrosamine-free losartan for patients.

FDA reminds patients taking recalled losartan to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition. Untreated hypertension (high blood pressure) leads to an increase in the risk of heart attacks and stroke. Untreated heart failure increases the risk of hospitalization and death. Untreated diabetic nephropathy (kidney disease) leads to worsening renal (kidney) disease.

Manufacturers should contact FDA's Drug Shortages Staff when their testing of losartan shows levels of NMBA that exceed the interim acceptable intake limit of 0.96 ppm. FDA will determine, on a case-by-case basis, whether lots containing NMBA greater than 0.96 ppm should be released for distribution.

FDA continues to work with companies and international regulators to ensure products entering the U.S. market do not contain nitrosamine impurities.

3/1/2019: UPDATE - Torrent again expands its voluntary recall of losartan; Hetero also voluntarily recalls losartan

Update [3/1/2019] Torrent Pharmaceuticals Limited is further expanding its voluntary recall (Updated: Torrent Pharmaceuticals Limited Issues Voluntary Nationwide Recall of Losartan Potassium Tablets, USP and Losartan Potassium /Hydrochlorothiazide Tablets, USP) [↗](http://www.fda.gov/about-fda/website-policies/website-disclaimer) (<http://www.fda.gov/about-fda/website-policies/website-disclaimer>) to include 114 additional lots of losartan potassium and losartan potassium/hydrochlorothiazide combination tablets. This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient manufactured by Hetero Labs Limited.

Today, the agency also issued a press release (FDA provides update on its ongoing investigation into ARB drug products; reports on finding of a new nitrosamine impurity in certain lots of losartan and product recall) to provide additional information about its ongoing investigation and another voluntary recall by Hetero/Camber Pharmaceuticals, which was announced on February 28, of 87 lots of losartan potassium tablets (25 mg, 50 mg and 100 mg). The recalled losartan potassium and losartan potassium/hydrochlorothiazide tablets are also manufactured by Hetero, which are distributed by Camber, and contain the impurity NMBA.

Torrent and Hetero/Camber are only recalling lots of losartan-containing medication with NMBA above the interim acceptable intake limits of 0.96 parts per million (ppm).

The agency also updated the list of losartan products under recall (</media/119422/download>).

3/1/2019: UPDATE - Aurobindo expands its voluntary recall of valsartan and amlodipine/valsartan

Update [3/1/2019] AurobindoPharma USA is expanding its voluntary recall (AurobindoPharma USA, Inc. Initiates a Voluntary Nationwide Consumer Level Recall Expansion of 38 Lots of Amlodipine Valsartan Tablets USP and Valsartan Tablets, USP due to the detection of NDEA (N-Nitrosodiethylamine) Impurity.) to include 38 additional lots of valsartan and amlodipine/valsartan combination tablets. The recall is due to unacceptable amounts of N-Nitrosodiethylamine (NDEA) found in the medicine.

Aurobindo is only recalling lots of valsartan-containing medication where NDEA has been detected above the interim acceptable intake limit of 0.083 parts per million. FDA is working with manufacturers to reduce and remove nitrosamines from angiotensin II receptor blockers (ARBs).

The agency also updated the valsartan products under recall (/media/118231/download).

3/1/2019: PRESS RELEASE - FDA provides update on its ongoing investigation into ARB drug products; reports on finding of a new nitrosamine impurity in certain lots of losartan and product recall

Go to Press Release

(<https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm632425.htm>).

FDA updates table of interim limits for nitrosamine impurities in ARBs

Update [2/28/2019] FDA is posting the updated table of interim acceptable intake limits for nitrosamine impurities to reflect N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) limits, which are the same as those for NDMA.

The agency will use the interim limits below to recommend manufacturers conduct a voluntary recall if laboratory testing confirms the presence of nitrosamine impurities in finished drug product. FDA is working with industry and international regulators to ensure products entering the market do not contain these impurities, but we are tolerating the impurities below the level established in the table for a short period of time to avoid a possible shortage of ARBs.

Not all ARB products contain NDMA, NDEA or NMBA impurities, so pharmacists may be able to provide an alternative medication not affected by the recalls, or health care professionals may prescribe a different medication that treats the same condition.

Interim Limits for NDMA, NDEA, and NMBA in Angiotensin II Receptor Blockers (ARBs)

Drug	Maximum Daily Dose (mg/day)	Acceptable Intake NDMA (ng/day)*	Acceptable Intake NDMA (ppm)**	Acceptable Intake NDEA (ng/day)*	Acceptable Intake NDEA (ppm)**	Acceptable Intake NMBA (ng/day)*	Acceptable Intake NMBA (ppm)**
Valsartan	320	96	0.3	26.5	0.083	96	0.3
Losartan	100	96	0.96	26.5	0.27	96	0.96***
Irbesartan	300	96	0.32	26.5	0.088	96	0.32
Azilsartan	80	96	1.2	26.5	0.33	96	1.2
Olmesartan	40	96	2.4	26.5	0.66	96	2.4
Eprosartan	800	96	0.12	26.5	0.033	96	0.12
Candesartan	32	96	3.0	26.5	0.83	96	3.0
Telmisartan	80	96	1.2	26.5	0.33	96	1.2

* The acceptable intake is a daily exposure to a compound such as NDMA, NDEA, or NMBA that approximates a 1:100,000 cancer risk after 70 years exposure

** These values are based on a drug's maximum daily dose as reflected in the drug label

*** FDA is temporarily not objecting to losartan with NMBA below 9.82 ppm remaining on the market

2/25/2019: UPDATE - Losartan distributed by Macleods Pharmaceuticals voluntarily recalled

Update [2/25/2019] FDA is alerting patients and health care professionals to a voluntary recall of one lot of losartan potassium/hydrochlorothiazide (HCTZ) 100mg/25mg combination tablets manufactured by Macleods Pharmaceuticals. The recall is due to unacceptable amounts of N-Nitrosodiethylamine (NDEA) found in the medicine made with active pharmaceutical ingredient manufactured by Hetero Labs Limited.

Macleods is only recalling lots of losartan-containing medication where NDEA has been detected above the interim acceptable intake limit of 0.27 parts per million. FDA is working with manufacturers to reduce and remove nitrosamines from angiotensin II receptor blockers (ARBs).

The agency also updated the list of losartan products under recall (</media/119422/download>).

1/25/2019: STATEMENT - Statement from FDA Commissioner Scott Gottlieb, M.D., and Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research on the FDA's ongoing investigation into valsartan and ARB class impurities and the agency's steps to address the root causes of the safety issues

Go to [FDA Statement \(/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-and-arb-class-impurities-and-agencys-steps\)](/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-and-arb-class-impurities-and-agencys-steps).

1/23/2019: UPDATE - Torrent further expands its voluntary recall of losartan

Update [1/23/2019] Torrent Pharmaceuticals is further expanding its voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall-losartan-potassium) to include six additional lots of losartan potassium and hydrochlorothiazide combination tablets, for a total of 16 lots of losartan-containing medicines. This recall is due to unacceptable amounts of N-Nitrosodiethylamine (NDEA) in the losartan active pharmaceutical ingredient manufactured by Hetero Labs Limited.

Torrent is only recalling lots of losartan-containing medication containing NDEA above the interim acceptable intake limits of 0.27 parts per million (ppm).

The agency also updated the list of losartan medications under recall (/media/119422/download).

1/18/2019: UPDATE - Irbesartan distributed by Solco Healthcare voluntarily recalled

Update [1/18/2019] FDA is alerting patients and health care professionals to a voluntary recall (/safety/recalls-market-withdrawals-safety-alerts/prinston-pharmaceutical-inc-issues-voluntary-nationwide-recall-irbesartan-and-irbesartan-hctz) of one lot of irbesartan and seven lots of irbesartan and hydrochlorothiazide (HCTZ) combination tablets distributed by Solco Healthcare LLC, a Princeton Pharmaceutical Inc. subsidiary. The recall is due to unacceptable amounts of N-Nitrosodiethylamine (NDEA) in the irbesartan active pharmaceutical ingredient manufactured by Zhejiang Huahai Pharmaceuticals (ZHP).

Solco is only recalling lots of irbesartan-containing medication where NDEA has been detected above the interim limit of 0.088 parts per million. FDA is working with manufacturers to reduce and remove nitrosamines from angiotensin receptor II blockers (ARBs).

The agency also updated the list of irbesartan products under recall.

1/3/2019: UPDATE - Torrent expands its voluntary recall of losartan

Update [1/3/2019] Torrent Pharmaceuticals is expanding its voluntary [recall](/safety/recalls-market-withdrawals-safety-alerts/torrent-pharmaceuticals-limited-expands-voluntary-nationwide-recall-losartan-potassium-tablets-usp) (</safety/recalls-market-withdrawals-safety-alerts/torrent-pharmaceuticals-limited-expands-voluntary-nationwide-recall-losartan-potassium-tablets-usp>) to include eight additional lots of losartan potassium tablets, for a total of 10 lots. This recall is due to trace amounts of N-Nitrosodiethylamine (NDEA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited.

Torrent is only recalling lots of losartan medication containing NDEA above the interim [acceptable intake](#) level of 0.27 parts per million.

The agency also updated the list of [list of valsartan products under recall](#) (</media/118231/download>).

1/2/2019: UPDATE - FDA alerts patients and health care professionals to Aurobindo's recall of valsartan medication due to NDEA

Update [1/2/2019] FDA is alerting patients and health care professionals to Aurobindo Pharma USA's voluntary [recall](/safety/recalls-market-withdrawals-safety-alerts/aurobindo-pharma-usa-inc-initiates-voluntary-nationwide-consumer-level-recall-80-lots-amlodipine) (</safety/recalls-market-withdrawals-safety-alerts/aurobindo-pharma-usa-inc-initiates-voluntary-nationwide-consumer-level-recall-80-lots-amlodipine>) of two lots of valsartan tablets, 26 lots of amlodipine and valsartan combination tablets, and 52 lots of valsartan and hydrochlorothiazide (HCTZ) combination tablets due to the amount of N-Nitrosodiethylamine (NDEA) in the valsartan active pharmaceutical ingredient. Aurobindo is recalling amlodipine and HCTZ only in combination medications containing valsartan. Neither amlodipine nor HCTZ is currently under recall by itself.

Aurobindo is recalling lots of valsartan-containing medication that tested positive for NDEA above the interim [acceptable daily intake](#) level of 0.083 parts per million.

The agency continues to investigate and test all angiotensin II receptor blockers (ARBs) for the presence of NDEA and N-Nitrosodimethylamine (NDMA) and is taking swift action when it identifies these impurities that are above interim acceptable daily intake levels.

FDA also updated the [list of valsartan products under recall](#) (</media/118231/download>) and the [list of valsartan products not under recall](#) (</media/118232/download>).

FDA reminds patients taking any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition. Some ARBs contain no NDMA or NDEA.

12/20/2019: UPDATE - FDA alerts patients and health care professionals to Torrent's recall of losartan medication due to NDEA

Update [12/20/2018] FDA is alerting patients and health care professionals to Torrent Pharmaceuticals'

voluntary recall (</safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall-losartan-potassium>) of two lots of losartan potassium 100 mg tablets due to N-Nitrosodiethylamine (NDEA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited.

Not all Torrent losartan-containing medications distributed in the U.S. are being recalled. Torrent is recalling only those lots of losartan medication that tested positive for NDEA above the acceptable daily intake of 0.27 ppm.

The agency continues to investigate and test all angiotensin II receptor blockers (ARBs) for the presence of NDEA and N-Nitrosodimethylamine (NDMA) and is taking swift action when it identifies these impurities that are above acceptable daily intake levels.

FDA posted a list of [losartan medications under recall \(/media/119422/download\)](/media/119422/download). Additionally, FDA reminds patients taking this medication or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know not all ARBs contain NDMA or NDEA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

12/19/2018: UPDATE - FDA presents interim limits of nitrosamines in currently marketed ARBs

Update [12/19/2018] FDA is publishing interim acceptable intake levels of nitrosamine impurities in angiotensin II receptor blockers (ARBs) for manufacturers to use to ensure their finished drug products are safe for patients.

The agency evaluated safety data for N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) to determine an interim acceptable intake level for these impurities in the ARB class. NDMA and NDEA are probable human carcinogens and should

not be present in drug products. We are currently aware of NDMA and NDEA in certain valsartan, irbesartan and losartan-containing products, and those products and some active pharmaceutical ingredients (API) used to manufacture them have been recalled from the U.S. market. See the [list of valsartan products under recall \(/media/118231/download\)](/media/118231/download) and the [list of irbesartan products under recall \(/media/118233/download\)](/media/118233/download).

Drug products that contain NDMA or NDEA above the limits in the table below pose an unacceptable risk to patients. The agency will use the interim limits to recommend manufacturers conduct a voluntary recall if laboratory testing confirms the presence of nitrosamine impurities in finished drug product. FDA is working with industry and international regulators to ensure products entering the market do not contain these impurities, but we are tolerating the impurities below the level established in the table for a short period of time to avoid a possible shortage of ARBs.

The agency reminds manufacturers they are responsible for developing and using suitable methods to detect impurities, including when they make changes to their manufacturing processes. If a manufacturer detects a new impurity or higher level of impurities, they should fully evaluate the impurities and take action to ensure the product is safe for patients. To aid industry and regulatory agencies, FDA has developed and published methods to detect NDMA and NDEA impurities – the gas chromatography/mass spectrometry (GC/MS) headspace method (</media/115965/download>), the [combined GC/MS headspace method \(/media/117843/download\)](/media/117843/download), and the [combined GC/MS direct injection method \(/media/117807/download\)](/media/117807/download). These methods can be used for drug substances and products, and users should validate them as part of good manufacturing practices and where data are used to support a regulatory submission or required quality assessment of the API or drug product.

Not all ARB products contain NDMA or NDEA impurities, so pharmacists may be able to provide an alternative medication not affected by the recalls, or health care professionals may prescribe a different medication that treats the same condition.

Interim Limits for NDMA and NDEA in Angiotensin II Receptor Blockers (ARBs)

Drug	Maximum Daily Dose (mg/day)	Acceptable Intake NDMA (ng/day)*	Acceptable Intake NDMA (ppm)**	Acceptable Intake NDEA (ng/day)*	Acceptable Intake NDEA (ppm)**
Valsartan	320	96	0.3	26.5	0.083
Losartan	100	96	0.96	26.5	0.27
Irbesartan	300	96	0.32	26.5	0.088

Azilsartan	80	96	1.2	26.5	0.33
Olmesartan	40	96	2.4	26.5	0.66
Eprosartan	800	96	0.12	26.5	0.033
Candesartan	32	96	3.0	26.5	0.83
Telmisartan	80	96	1.2	26.5	0.33

* The acceptable intake is a daily exposure to a compound such as NDMA or NDEA that results in a 1:100,000 cancer risk after 70 years exposure

** These values are based on a drug's maximum daily dose as reflected in the drug label

For comparison with the levels of NDMA found in some common foods, please see our Aug. 20, 2018, update.

12/12/2018: UPDATE - FDA updates NDMA and NDEA detection methods, announces posting of ZHP warning letter

Update [12/12/2018] The FDA has updated its testing methods to detect NDMA and NDEA impurities – the [GC/MS\) headspace method \(/media/115965/download\)](#), the [combined headspace method \(/media/117843/download\)](#), and the [combined direct injection method \(/media/117807/download\)](#) – by adding the limits of detection (LOD) and clarifying that the methods can be used for both drug substances and drug products. These methods were validated with respect to valsartan drug substances and drug products, but the agency expects them to have comparable LODs and limits of quantitation (LOQ) for other angiotensin II receptor blockers (ARB).

The agency also issued a press release announcing the posting of a warning letter the agency issued Nov. 29 to Zhejiang Huahai Pharmaceuticals Co. Ltd. (ZHP).

12/11/2018: PRESS RELEASE - FDA warns API manufacturer involved in valsartan recall, provides information for patients taking these medications

Go to [Press Release \(/news-events/press-announcements/fda-warns-api-manufacturer-involved-valsartan-recall-provides-information-patients-taking-these\)](#).

12/6/2018: UPDATE - Mylan expands its voluntary recall of valsartan-containing products

Update [12/6/2018] Mylan Pharmaceuticals is expanding its voluntary recall ([!-\$wcmUrl('link','UCM627647')--]) to include all lots of non-expired valsartan-containing products due to trace amounts of N-Nitrosodiethylamine (NDEA) in the valsartan active pharmaceutical ingredient (API) manufactured by Mylan Laboratories Limited. The 104 additional lots include 26 lots of amlodipine and valsartan tablets, 51 lots of valsartan tablets and 27 lots of valsartan and hydrochlorothiazide tablets. These lots were distributed in the U.S. between March 2017 and November 2018.

The agency also updated the [list of valsartan products under recall \(/media/118231/download\)](/media/118231/download) and the [list of valsartan products not under recall \(/media/118232/download\)](/media/118232/download).

11/27/2018: UPDATE - FDA alerts patients and health care professionals to Teva's recall of valsartan products due to NDEA

Update [11/27/2018] FDA is alerting patients and health care professionals to Teva Pharmaceuticals' voluntary [recall \(/safety/recalls-market-withdrawals-safety-alerts\)](/safety/recalls-market-withdrawals-safety-alerts) of valsartan-containing products manufactured using active pharmaceutical ingredient (API) from Mylan Pharmaceuticals. Mylan voluntarily [recalled \(/safety/recalls-market-withdrawals-safety-alerts\)](/safety/recalls-market-withdrawals-safety-alerts) valsartan-containing products on November 20.

Teva is recalling all lots of amlodipine and valsartan combination tablets and amlodipine, valsartan, and hydrochlorothiazide (HCTZ) combination tablets due to the presence of N-Nitrosodiethylamine (NDEA). Teva has recalled other valsartan-containing products in recent months due to the presence of N-Nitrosodimethylamine (NDMA). With this recall, Teva has now recalled all their unexpired valsartan-containing products from the U.S. market.

The agency continues to investigate and test all angiotensin II receptor blocker (ARBs) for the presence of NDMA and NDEA and is taking swift action when it identifies these impurities that are above acceptable levels.

FDA has updated the [list of valsartan products under recall \(/media/118231/download\)](/media/118231/download) and the [list of valsartan products not under recall \(/media/118232/download\)](/media/118232/download). The agency reminds patients taking this medication or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know that not all ARBs contain NDMA or NDEA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

11/21/2018: UPDATE - FDA alerts patients and health care professionals to Mylan's recall of valsartan products due to NDEA

Update [11/21/2018] FDA is alerting patients and health care professionals to Mylan Pharmaceuticals' voluntary recall of 15 lots of valsartan-containing products due to the presence of N-Nitrosodiethylamine (NDEA).

Not all Mylan valsartan-containing products distributed in the U.S. are being recalled. Mylan is recalling only those lots of valsartan-containing products that tested positive for NDEA above the acceptable level. The agency continues to investigate and test all angiotensin II receptor blockers (ARBs) for the presence of NDEA and N-Nitrosodimethylamine (NDMA) and is taking swift action when it identifies these impurities that are above acceptable levels.

FDA has updated lists of [valsartan products under recall \(/media/118231/download\)](/media/118231/download) and [valsartan products not under recall \(/media/118232/download\)](/media/118232/download). Additionally, FDA reminds patients taking this medication or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know not all ARBs contain NDMA or NDEA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

11/9/2018: UPDATE - FDA alerts patients and health care professionals to Sandoz's losartan potassium and hydrochlorothiazide recall of one lot due to NDEA

Update [11/9/2018] FDA is alerting patients and health care professionals to Sandoz's voluntary recall (</safety/recalls-market-withdrawals-safety-alerts/sandoz-inc-issues-voluntary-nationwide-recall-one-lot-losartan-potassium-and-hydrochlorothiazide-due>) of one lot – JB8912 – of losartan potassium and hydrochlorothiazide 100mg/25mg tablets, that contain losartan, an angiotensin II receptor blocker (ARB), and hydrochlorothiazide, a diuretic, used in combination for the treatment of hypertension. Sandoz's product was made using an active pharmaceutical ingredient (API) that has tested positive for NDEA. The API was manufactured by Zhejiang Huahai Pharmaceutical Co. Ltd, which is on import alert (https://www.accessdata.fda.gov/cms_ia/importalert_189.html).

Sandoz's losartan drug products make up less than 1 percent of the total losartan drug products in the U.S. market.

FDA continues to investigate the presence of NDEA and NDMA, which are probable human carcinogens, in ARBs and is taking swift action when it identifies unacceptable impurities in API and finished drug products.

FDA reminds patients taking this medication or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know not all ARBs contain NDEA or NDMA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

10/30/2018: UPDATE - FDA alerts patients and health care professionals to ScieGen's irbesartan recall due to NDEA

Certain irbesartan products labeled as Westminster Pharmaceuticals Inc. and GSMS Inc. recalled

Update [10/30/2018] FDA is alerting patients and health care professionals to ScieGen's voluntary recall of certain lots of irbesartan, an angiotensin II receptor blocker (ARB), because they contain N-Nitrosodiethylamine (NDEA), a known animal and suspected human carcinogen (causes cancer). FDA laboratory testing confirmed NDEA in some lots of ScieGen's irbesartan. ScieGen's irbesartan products are labeled as Westminster Pharmaceuticals and Golden State Medical Supply, Inc. (GSMS). See the [list of irbesartan products under recall \(/media/117814/download\)](/media/117814/download). This is the first non-valsartan drug product the agency has found to contain the NDEA impurity.

ScieGen's recall affects about 1 percent of the irbesartan drug products in the U.S. market.

Additionally, Aurobindo, which manufactures the active pharmaceutical ingredient (API) for ScieGen's irbesartan products, is [recalling \(/safety/recalls-market-withdrawals-safety-alerts/aurobindo-pharma-limited-issues-voluntary-recall-irbesartan-drug-substance-due-detection-trace\)](/safety/recalls-market-withdrawals-safety-alerts/aurobindo-pharma-limited-issues-voluntary-recall-irbesartan-drug-substance-due-detection-trace) all unexpired lots of its irbesartan API supplied to the U.S. market with NDEA. FDA and Aurobindo laboratory testing confirmed NDEA in certain lots of their irbesartan API.

FDA reminds patients taking any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. Not all ARBs contain NDEA or N-Nitrosodimethylamine (NDMA), a probable human carcinogen previously found in certain recalled valsartan products, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

To date, ScieGen is the only manufacturer of irbesartan drug products found to contain NDEA. FDA continues to test all ARBs for the presence of impurities and has publicly posted two methods for manufacturers and regulatory agencies around the world to test their ARBs for the unexpected NDMA and NDEA impurities. The [combined headspace](#)

method (/media/117843/download) and the combined direct injection method (/media/117807/download) can detect and quantify NDMA and NDEA simultaneously in ARB API and finished drug products.

FDA continues to work with API and drug manufacturers to ensure their products are not at risk for NDMA or NDEA formation. The agency reminds manufacturers they are responsible for developing and using suitable methods to detect impurities, including when they make changes to their manufacturing processes. If a manufacturer detects new or higher levels of impurities, they should fully evaluate the impurities and take action to ensure the product is safe for patients.

For additional information about ARB products, see:

- list of valsartan products under recall (/media/118231/download)
- list of valsartan products not under recall (/media/118232/download)

10/24/2018: UPDATE - FDA updates recalled valsartan-containing product information

Update [10/24/2018] FDA continues to evaluate valsartan-containing products and other angiotensin II receptor blockers (ARBs), and has updated the list of products included in the recall (/media/118231/download) to add one additional lot of RemedyRepack.

10/16/2018: UPDATE - FDA releases additional NDMA/NDEA detection method

Update [10/16/2018] FDA is posting a gas chromatography-tandem mass spectrometry (GC-MS/MS) method (/media/117807/download) utilizing liquid injection for detecting the presence of impurities N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) in valsartan drug products.

This method provides an additional option for regulators and industry to detect NDMA and NDEA impurities. This method can be used alone or in combination with the combined gas chromatography-mass spectrometry (GC/MS) headspace method (/media/117843/download) the agency recently posted. Like the previously posted methods, this method should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

10/11/2018: UPDATE - FDA releases method for detection and quantification of both NDMA and NDEA

Update [10/11/2018]] FDA is posting a redeveloped combined gas chromatography-mass spectrometry (GC/MS) [headspace \(/media/117843/download\)](/media/117843/download) method for detecting the presence of impurities N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) in valsartan drug products.

FDA previously posted a GC/MS method for detection of NDMA in valsartan products. Upon detection of NDEA in valsartan products manufactured by Zhejiang Huahai Pharmaceuticals, FDA redeveloped the testing method so that it can be used to detect and quantify levels of both NDMA and NDEA. This method should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

FDA is also working on a GC/MS direct injection method for detection of NDMA and NDEA. We will post the method when it is available. This will provide an additional option for regulators and industry to use to detect both impurities.

10/5/2018: UPDATE - FDA posts laboratory analysis of NDMA levels in recalled valsartan products

Update [10/5/2018] FDA posted laboratory test results showing NDMA levels in recalled valsartan products. FDA will also post [test results \(/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products\)](/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products) and an assessment of the cancer risk from NDEA when they are available.

9/28/2018: UPDATE - FDA places Zhejiang Huahai Pharmaceuticals on import alert

Update [9/28/2018] FDA placed Zhejiang Huahai Pharmaceuticals on [import alert \(https://www.accessdata.fda.gov/cms_ia/importalert_189.html\)](https://www.accessdata.fda.gov/cms_ia/importalert_189.html) on September 28, 2018, to protect U.S. patients while the active pharmaceutical ingredient (API) manufacturer fully determines how impurities were introduced into its API and remediates its quality systems. The import alert stops all API made by ZHP and finished drug products made using ZHP's API from legally entering the United States. FDA's action follows a recent [inspection \(/media/117875/download\)](/media/117875/download) at ZHP's facility.

FDA reminds manufacturers that it is their responsibility to develop and use suitable methods to detect impurities, including when they make changes to their manufacturing processes. If a manufacturer detects new or higher levels of impurities, they should fully evaluate the impurities and take action to ensure the product is safe for patients.

9/24/2018: UPDATE - FDA updates recall lists and releases method for the detection and quantification of NDMA in valsartan

Update [9/24/2018] FDA has updated the [list of valsartan products not under recall \(/media/118232/download\)](/media/118232/download) with five Teva products that were not previously on either list.

9/13/2018: PRESS RELEASE - FDA provides update on its ongoing investigation into valsartan products; and reports on the finding of an additional impurity identified in one firm's already recalled products

Go to [Press Release \(/news-events/press-announcements/fda-provides-update-its-ongoing-investigation-valsartan-products-and-reports-finding-additional\)](/news-events/press-announcements/fda-provides-update-its-ongoing-investigation-valsartan-products-and-reports-finding-additional).

8/30/2018: STATEMENT - Statement from FDA Commissioner Scott Gottlieb, M.D., and Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research on FDA's ongoing investigation into valsartan impurities and recalls and an update on FDA's current findings

Go to [FDA Statement \(/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current\)](/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current).

8/24/2018: UPDATE - FDA updates recall lists

Update [8/24/2018] Torrent Pharmaceuticals Limited is expanding its voluntary [recall \(/safety/recalls-market-withdrawals-safety-alerts/updatedadditional-lots-added-torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall\)](/safety/recalls-market-withdrawals-safety-alerts/updatedadditional-lots-added-torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall). FDA has updated the [list of valsartan products under recall \(/media/118231/download\)](/media/118231/download).

8/22/2018: UPDATE - FDA updates recall lists and releases method for the detection and quantification of NDMA in valsartan

Update [8/22/2018] Torrent Pharmaceuticals Limited is expanding its voluntary recall to all lots of unexpired valsartan-containing drug products due to the detection of NDMA in the active pharmaceutical ingredient (API) manufactured by Zhejiang Huahai

Pharmaceuticals.

RemedyRepack, a repackager of Torrent's valsartan/amlodipine/hydrochlorothiazide (HCTZ) tablets, has also recalled.

FDA has updated the [list of valsartan products under recall \(/media/118231\)](/media/118231) and the [list of valsartan products not under recall \(/media/118232/download\)](/media/118232/download).

Additionally, FDA is releasing a gas chromatography-mass spectrometry (GC/MS) [headspace method \(/media/115965/download\)](/media/115965/download) for manufacturers and regulators to detect and quantify NDMA in valsartan API and finished drug products. The agency is using this method to test potential NDMA-containing APIs and drug products. This method should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

8/20/2018: UPDATE - FDA updates recalled valsartan-containing product information and presents NDMA levels in some foods

Update [8/20/2018] FDA is alerting health care professionals and patients that Torrent Pharmaceuticals Limited is voluntarily [recalling \(/safety/recalls-market-withdrawals-safety-alerts/torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall-valsartan-amlodipine-hctz-tablets\)](/safety/recalls-market-withdrawals-safety-alerts/torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall-valsartan-amlodipine-hctz-tablets) 14 lots of valsartan/amlodipine/hydrochlorothiazide (HCTZ) tablets. Not all Torrent valsartan products distributed in the U.S. are being recalled.

FDA recently learned Torrent used affected valsartan active pharmaceutical ingredient (API) manufactured by Zhejiang Huahai Pharmaceuticals. FDA testing confirmed NDMA in some Torrent products.

To date, Torrent has not received any reports of adverse events related to this recall.

FDA has updated the [list of valsartan products under recall \(/media/118231\)](/media/118231) and the [list of valsartan products not under recall \(/media/118232/download\)](/media/118232/download) to incorporate additional repackagers of Camber's valsartan products and Torrent's recall.

NDMA is a known environmental contaminant. For context, it is found in water and foods including meats, dairy products and vegetables.

**Estimated Range of Daily NDMA Consumption for certain foods
(Recommended daily food consumption rates based on [Dietary Guidelines for Americans 2015-2020](https://health.gov/dietaryguidelines/2015/guidelines/) (<https://health.gov/dietaryguidelines/2015/guidelines/>))**

- Cured meat - 0.004-0.23 micrograms¹

- Smoked meat - 0.004-1.02 micrograms¹
- Grilled meat - 0.006-0.13 micrograms¹
- Bacon - 0.07-0.09 micrograms²
 - In more ordinary terms, for example, one pound of bacon may contain 0.304-0.354 micrograms of NDMA

FDA reminds patients taking valsartan from a recalled lot that they should continue taking their current medicine until their doctor or pharmacist provides a replacement or a different treatment option. Not all valsartan products contain NDMA, so pharmacists may be able to provide a refill of valsartan medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

¹ Mavelle, T., B. Bouchikhi, and G. Debry, *The occurrence of volatile N-nitrosamines in French foodstuffs. Food Chemistry*, 1991. 42(3): p. 321-338.

² Park, J., et al., *Distribution of Seven N-Nitrosamines in Food. Toxicol Res*, 2015. 31(3): p. 279-288.

8/9/2018: UPDATE - FDA updates recalled valsartan-containing product information

Update [8/9/2018] FDA has updated the [list of valsartan products under recall \(/media/118231\)](/media/118231) and the [list of valsartan products not under recall \(/media/118232/download\)](/media/118232/download) to incorporate recalls of valsartan-containing products manufactured by Hetero Labs Limited, in India, labeled as Camber Pharmaceuticals Inc. Not all Camber valsartan products distributed in the U.S. are being recalled.

Camber Pharmaceuticals is [recalling \(/safety/recalls-market-withdrawals-safety-alerts/camber-pharmaceuticals-inc-issues-voluntary-nationwide-recall-valsartan-tablets-usp-40mg-80mg-160mg\)](/safety/recalls-market-withdrawals-safety-alerts/camber-pharmaceuticals-inc-issues-voluntary-nationwide-recall-valsartan-tablets-usp-40mg-80mg-160mg) certain valsartan tablets because they contain the impurity N-nitrosodimethylamine (NDMA) in the active pharmaceutical ingredient (API). Hetero Labs manufactures the API for the Camber products using a process similar to Zhejiang Huahai Pharmaceuticals.

Test results from Hetero Labs show the amount of NDMA found in its valsartan API exceeds acceptable levels; although it is generally lower than the amount discovered in the API manufactured by Zhejiang.

FDA is testing samples of valsartan API and finished products to confirm the extent and amount of NDMA and help inform the ongoing investigation. The agency has also contacted other manufacturers of valsartan API to determine if their manufacturing processes are at risk for the formation of NDMA, and is working with them to ensure NDMA is not present in future valsartan API.

Valsartan is an angiotensin II receptor blocker (ARB), and FDA is investigating whether other types of ARBs are at risk for the presence of NDMA.

Recalled valsartan products labeled as Camber may be repackaged by other companies. FDA will provide updates as more information becomes available.

8/2/2018: UPDATE - FDA updates recalled valsartan-containing product information and reminds API manufacturers to evaluate processes for unsafe impurities

Update [8/2/2018] FDA continues to evaluate valsartan-containing products and has updated the [list of products included in the recall \(/media/118231/download\)](/media/118231/download) and the [list of products not included in the recall \(/media/118232/download\)](/media/118232/download). In addition to updating the lists, FDA revised information related to A-S Medication on the list of products included in the recall. The agency will continue to provide information when it becomes available.

FDA is working with drug manufacturers to ensure future valsartan active pharmaceutical ingredients (APIs) are not at risk of NDMA formation. The agency reminds manufacturers to thoroughly evaluate their API manufacturing processes, and changes to those processes, to detect any unsafe impurities. If a manufacturer detects new or higher levels of impurity, they should take action to prevent changes to the product's safety profile.

7/27/2018: UPDATE - FDA updates recalled valsartan-containing product information

Update [7/27/2018] FDA is updating health care professionals and patients after discovering that several additional companies that repackage drug products are also recalling valsartan-containing products.

FDA has product recall information from three additional repackagers of valsartan-containing products made by Teva Pharmaceuticals and Princeton Pharmaceuticals Inc. – labeled as A-S Medication Solutions LLC, AvKARE and RemedyRepack – and the agency has added them to the recalled products list. Two of these companies, A-S Medication and RemedyRepack, may also distribute valsartan products not affected by the recall. The agency is confirming this information and will provide an update once it is available.

The following additional repackagers are recalling or are expected to recall valsartan-containing products. FDA is working to gather product recall information from these companies and has removed them from the list of products that are not impacted by this recall:

- Bryant Ranch Prepack Inc.
- H. J. Harkins Company Inc. (*this company was not originally included on either list*)
- Lake Erie Medical, doing business as Quality Care Products LLC
- NuCare Pharmaceuticals Inc.
- Northwind Pharmaceuticals
- Proficient Rx

It is possible that not all valsartan-containing products repackaged by these companies are impacted by the recall. **FDA continues to evaluate valsartan-containing products** and will update the [list of products included in the recall \(/media/118231/download\)](/media/118231/download) and the [list of products not included in the recall \(/media/118232/download\)](/media/118232/download) as more information becomes available.

7/27/2018: UPDATE - Analysis of N-nitrosodimethylamine (NDMA) Levels in Recalled Valsartan in the U.S.

Update [7/27/2018] On July 13th, FDA announced a recall of certain batches of valsartan tablets because of an impurity, a chemical known as N-nitrosodimethylamine (NDMA). Valsartan is a medication commonly used to treat high blood pressure and heart failure.

NDMA has been found to increase the occurrence of cancer in animal studies. These animal studies were done using amounts of NDMA much higher than the impurity levels in recalled valsartan batches. Based on these animal studies, the U.S. Environmental Protection Agency considers NDMA a probable human carcinogen (https://www.epa.gov/sites/production/files/2017-10/documents/ndma_fact_sheet_update_9-15-17_508.pdf)—a chemical that can increase the risk of cancer in humans. NDMA is found in some water supplies and in some foods¹. Consuming up to 96 nanograms NDMA/day is considered reasonably safe for human ingestion². It is estimated that over the course of a person's lifetime, consuming this amount of NDMA would result in less than one additional case of cancer for every 100,000 people. To put this in context, currently one out of every three people in the US will experience cancer in their lifetime.

The amounts of NDMA found in the recalled batches of valsartan exceeded these acceptable levels. The agency wanted to put some context around the actual potential risk posed to patients who used versions of valsartan that may have contained high levels of NDMA. Based on records from the manufacturer of the recalled valsartan, some levels of the impurity may have been in the valsartan-containing products for as long as four years. FDA scientists estimate that if 8,000 people took the highest valsartan dose (320 mg) from the recalled batches daily for the full four years, there may be one additional case of cancer over the lifetimes of these 8,000 people. This assessment led to FDA's decision to have these batches recalled.

Patients taking valsartan from a recalled batch should continue taking their current medicine until their doctor or pharmacist provides a replacement or a different treatment option. It is important to know that not all valsartan products contained NDMA, so pharmacists may be able to provide a refill of valsartan medication from batches that are not affected by the recall, or doctors may prescribe a different medication that treats the same indications.

FDA continues to evaluate the safety of valsartan-containing products and will update the [list of products included in the recall \(/media/118231/download\)](/media/118231/download) and the [list of products not included in the recall \(/media/118232/download\)](/media/118232/download) as more information becomes available. If you are taking a valsartan product, be sure to check to back as the lists may change.

¹ From Toxnet: <https://toxnet.nlm.nih.gov/> (<https://toxnet.nlm.nih.gov/>).

Average Daily Intake: WATER: (assume 3 to 6 ng N-nitrosodimethylamine/l)(1) 6 to 12 ng; direct intake from drinking water is probably much less than 1 ug/day(2). FOOD: (assume <0.1 to=" 84=" ug/kg)(4)=" <0.16 to=" 134="

[(1) Kimoto WI et al; Water Res 15: 1099-1106 (1981) (2) USEPA; Ambient Water Quality Criteria Doc: Nitrosamines p.C-14 (1980) EPA 440/5-80-064 (4) IARC; IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 17: 125-76 (1978)]

² The calculated acceptable intake for NDMA is based on methods described in the ICH Guidance M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (<http://wcms-internet.fda.gov/files/drugs/published/M7-R1-AssessmentAndControlOfDNA-Reactive-Mutagenic-ImpuritiesInPharmaceuticalsToLimitPotentialCarcinogenicRisk-Guidance.pdf>)

(<http://wcms-internet.fda.gov/files/drugs/published/M7-R1-AssessmentAndControlOfDNA-Reactive-Mutagenic-ImpuritiesInPharmaceuticalsToLimitPotentialCarcinogenicRisk-Guidance.pdf>))


7/24/2018: UPDATE - FDA publishes a list of valsartan-containing products not part of the recall

Update [7/24/2018] FDA is updating health care professionals and consumers on the agency's progress in responding to the ongoing recalls of valsartan, which is used to treat high blood pressure and heart failure, due to the presence of NDMA. The agency has posted a [list of valsartan-containing products not impacted \(/media/118232/download\)](/media/118232/download) by this recall. **FDA continues to evaluate valsartan-containing products** and will update the [list of products included in the recall \(/media/118231/download\)](/media/118231/download) and the [list of products not included in the recall \(/media/118232/download\)](/media/118232/download) as more information becomes available.

Manufacturers of these products often produce multiple dosage strengths, however not all of them are being recalled. FDA recommends health care professionals and patients carefully check these lists. Health care professionals and patients should check this statement frequently for any updates.

FDA reminds consumers to continue taking your current medicine until your doctor or pharmacist gives you a replacement or a different treatment option. Untreated hypertension (high blood pressure) leads to an increase in the risk of heart attacks and stroke. Untreated heart failure increases the risk of hospitalization and death.

Consumers and health care professionals should continue to report any adverse reactions with valsartan-containing products, to the [FDA's MedWatch program \(/medwatch-fda-safety-information-and-adverse-event-reporting-program\)](/medwatch-fda-safety-information-and-adverse-event-reporting-program) to help the agency better understand the scope of the problem:

- Complete and submit the report online at www.fda.gov/medwatch/report.htm (<https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home>).
- Download and complete the appropriate form, then submit it via fax at 1-800-FDA-0178 

7/18/2018: STATEMENT - FDA updates health care professionals and patients on recent valsartan recalls

[7/18/2018] The U.S. Food and Drug Administration is updating health care professionals and consumers following a recent [FDA press release \(/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity\)](#) about voluntary recalls of several drug products containing the active pharmaceutical ingredient (API) valsartan. Valsartan is used to treat high blood pressure and heart failure. Not all products containing valsartan are being recalled, and this update will clarify which valsartan-containing products are being recalled.

The recalled products contain an impurity, N-nitrosodimethylamine (NDMA), in the API manufactured by Zhejiang Huahai Pharmaceuticals, Linhai, China. The presence of the potentially cancer-causing NDMA was unexpected, and the agency believes the NDMA is related to changes in the way the active substance was manufactured. Some levels of the impurity may have been in the valsartan-containing products for as long as four years.

The investigation into valsartan-containing products is ongoing, and the following list may change. We will update this statement as we have more information.

There are currently three voluntary recalls related to the NDMA impurity detected in the valsartan API:

- **Teva Pharmaceuticals USA labeled as Major Pharmaceuticals** — recall is at the **retail level** because these products are only used in facilities where they are directly administered to patients by health care professionals: Valsartan 80 mg and 160 mg products;
- **Prinston Pharmaceuticals Inc. labeled as Solco Healthcare LLC** — recall is at the **consumer/user level**: Valsartan 40 mg, 80 mg, 160 mg, and 320 mg; and valsartan/HCTZ 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg, and 320 mg/25 mg products; and
- **Teva Pharmaceuticals labeled as Actavis LLC** — recall is at the **consumer/user level**: Valsartan 40 mg, 80 mg, 160 mg, and 320 mg; and valsartan/HCTZ 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg, and 320 mg/25 mg products.

[Detailed list of products included in the recall \(/media/118231/download\)](#) (PDF - 87 KB)

What should patients know:


- Continue taking your current medicine until your doctor or pharmacist gives you a replacement or a different treatment option.
- Not all valsartan-containing medications are affected and being recalled.

- If you are taking any medication containing valsartan, compare the information on your prescription bottle with [the information in this list \(/about-fda/page-not-found\)](/about-fda/page-not-found) (company, National Drug Code, lot number) to determine if your current medicine has been recalled. If you are not certain, contact your pharmacist.
- If you have medicine included in the recall, contact your pharmacist. The pharmacist may be able to provide you with valsartan made by another company. If not, contact your doctor immediately to discuss other treatment options.

What health care professionals should know:

- FDA has determined the recalled valsartan products pose an unnecessary risk to patients. Therefore, FDA recommends patients use valsartan-containing medicines made by other companies or consider other available treatment options for the patient's medical condition.
- If you have medication samples from these companies, quarantine the products and do not provide them to patients.

Consumers and health care professionals should report any adverse reactions with valsartan-containing products, to the FDA's [MedWatch program \(https://www.fda.gov/safety/medwatch/\)](https://www.fda.gov/safety/medwatch/) to help the agency better understand the scope of the problem:

- Complete and submit the report online at www.fda.gov/medwatch/report.htm (<https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home>).
- Download and complete the appropriate form, then submit it via fax at 1-800-FDA-0178 

7/13/2018: PRESS RELEASE - FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity

Go to [Press Release \(/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity\)](/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity).

FDA-published testing methods to provide options for regulators and industry to detect NDMA and NDEA impurities

The links below are to FDA-published testing methods to provide options for regulators and industry to detect nitrosamine impurities in ARB drug substances and drug products. These methods should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

- [Combined headspace method \(/media/117843/download\)](/media/117843/download): a GC/MS method that allows determination of both N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) simultaneously
- [Combined direct injection method \(/media/117807/download\)](/media/117807/download): a GC-MS/MS method that allows for determination of both NDMA and NDEA simultaneously
- [Direct injection GC-MS method \(/media/123409/download\)](/media/123409/download): a method that can detect NDMA, NDEA, N-Nitrosodiisopropylamine (NDIPA), N-Nitrosoethylisopropylamine (NEIPA), and N-nitrosodibutylamine (NDBA)
- [Headspace GC-MS method \(/media/124025/download\)](/media/124025/download): a method that can detect NDMA, NDEA, NDIPA, and NEIPA
- [LC-HRMS method \(/media/125478/download\)](/media/125478/download): a method that can detect NDMA, NDEA, NEIPA, NDIPA, NDBA, and N-Nitroso-N-methyl-4-aminobutyric acid (NMBA)
- [RapidFire-MS/MS method \(/media/125477/download\)](/media/125477/download): a method that can detect NEIPA, NDIPA, NDBA, and NMBA. We do not recommend using this method to detect NDMA or NDEA because it is less sensitive to those impurities.

The LC-HRMS and RapidFire-MS/MS methods are the first methods FDA has posted for detecting NMBA. The European Directorate for the Quality of Medicines (EDQM) has also published [methods to detect NDMA and NDEA \(https://www.edqm.eu/en/ad-hoc-projects-omcl-network\)](https://www.edqm.eu/en/ad-hoc-projects-omcl-network) [↗ \(http://www.fda.gov/about-fda/website-policies/website-disclaimer\)](http://www.fda.gov/about-fda/website-policies/website-disclaimer). FDA has not validated EDQM's methods.

Resources for You

- [Search ARBs Recalls List \(/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and-irbesartan\)](/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and-irbesartan)
- [Recalls of ARBs including Valsartan, Losartan and Irbesartan \(/drugs/drug-safety-and-availability/recalls-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and-irbesartan\)](/drugs/drug-safety-and-availability/recalls-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and-irbesartan)

- Nitrosamine Impurities in Medications (/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications).

Exhibit Q



N-Nitrosodimethylamine

CASRN 62-75-9 | DTXSID7021029

- [IRIS Summary \(PDF\)](#) (11 pp, 105 K)

[Key IRIS
Values](#)

[Other EPA
Information](#)

Noncancer Assessment

[Reference Dose for Oral Exposure \(RfD\) \(PDF\)](#) (11 pp, 105 K)

Not assessed under the IRIS Program.

Last Updated:

[Reference Concentration for Inhalation Exposure \(RfC\) \(PDF\)](#)

(11 pp, 105 K)

Not assessed under the IRIS Program.

Cancer Assessment

[Weight of Evidence for Cancer \(PDF\)](#) (11 pp, 105 K)

Last Updated: 01/31/1987

WOE Characterization	Framework for WOE Characterization
B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)	Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986)

Basis:

- Induction of tumors at multiple sites in both rodents and nonrodent mammals exposed by various routes.
- This may be a synopsis of the full weight-of-evidence narrative.

Quantitative Estimate of Carcinogenic Risk from Oral Exposure

(PDF) (11 pp, 105 K)

Oral Slope Factor: 5.1×10^1 per mg/kg-day

Drinking Water Unit Risk: 1.4×10^{-3} per $\mu\text{g/L}$

Extrapolation Method: Weibull, extra risk

Tumor site(s): Hepatic

Tumor type(s): Liver tumors (Peto et al., 1984)

Quantitative Estimate of Carcinogenic Risk from Inhalation

Exposure (PDF) (11 pp, 105 K)

Inhalation Unit Risk: 1.4×10^{-2} per $\mu\text{g/m}^3$

Extrapolation Method: Weibull, extra risk

Tumor site(s): Hepatic

Tumor type(s): Liver tumors (Peto et al., 1984)

You will need Adobe Reader to view some of the files on this page. See [EPA's PDF page](#) to learn more.

[Contact Us](#) to ask a question, provide feedback or report a problem.

Related Links

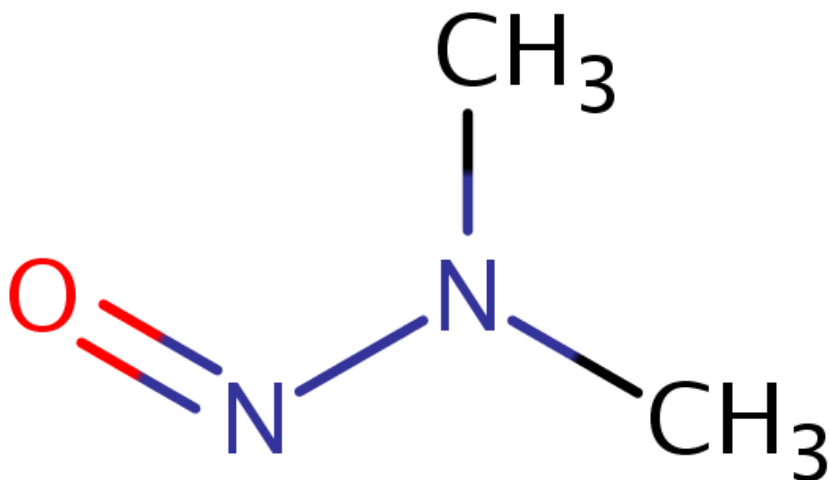
- [EPA Chemicals Dashboard - N-Nitrosodimethylamine](#)

Tumor Sites



Hepatic

Chemical Structure for N-Nitrosodimethylamine



Synonyms

- Dimethylamine, n-nitroso
- Dimethylnitrosamin
- Dimethylnitrosamine
- Dmna: dmn
- Methylamine, n-nitrosodi-

[more synonyms](#)

LAST UPDATED ON {MONTH DAY, YYYY}

Exhibit R



N-Nitrosodiethylamine

CASRN 55-18-5 | DTXSID2021028

- [IRIS Summary \(PDF\)](#) (11 pp, 106 K)

[Key IRIS
Values](#)

[Other EPA
Information](#)

Noncancer Assessment

[Reference Dose for Oral Exposure \(RfD\) \(PDF\)](#) (11 pp, 106 K)

Not assessed under the IRIS Program.

Last Updated:

[Reference Concentration for Inhalation Exposure \(RfC\) \(PDF\)](#)

(11 pp, 106 K)

Not assessed under the IRIS Program.

Cancer Assessment

[Weight of Evidence for Cancer \(PDF\)](#) (11 pp, 106 K)

Last Updated: 01/31/1987

WOE Characterization	Framework for WOE Characterization
B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)	Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986)

Basis:

- Induction of tumors at multiple sites in both rodent and nonrodent species exposed by various routes.
- This may be a synopsis of the full weight-of-evidence narrative.

Quantitative Estimate of Carcinogenic Risk from Oral Exposure
(PDF) (11 pp, 106 K)

Oral Slope Factor: 1.5×10^2 per mg/kg-day

Drinking Water Unit Risk: 4.3×10^{-3} per $\mu\text{g/L}$

Extrapolation Method: Weibull, extra risk

Tumor site(s): Hepatic

Tumor type(s): Liver tumors (Peto et al., 1984)

Quantitative Estimate of Carcinogenic Risk from Inhalation
Exposure (PDF) (11 pp, 106 K)

Inhalation Unit Risk: 4.3×10^{-2} per $\mu\text{g/m}^3$

Extrapolation Method: Weibull, extra risk

Tumor site(s): Hepatic

Tumor type(s): Liver tumors (Peto et al., 1984)

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Related Links

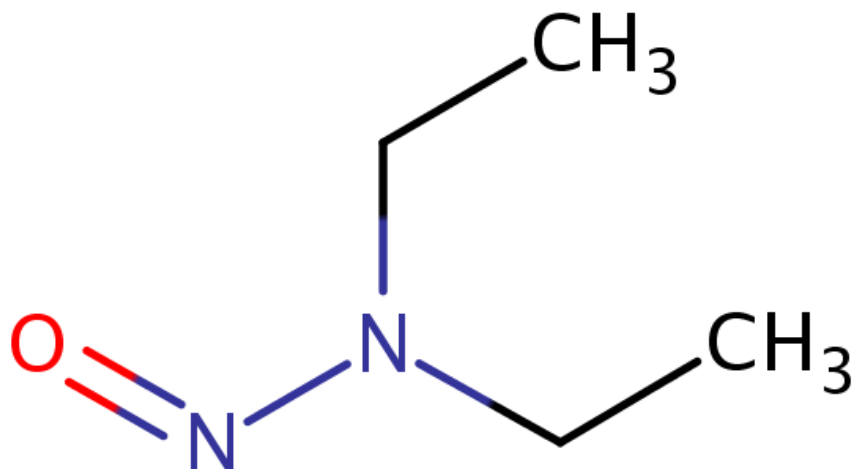
- [EPA Chemicals Dashboard - N-Nitrosodiethylamine](#)

Tumor Sites



Hepatic

Chemical Structure for N-Nitrosodiethylamine



Synonyms

- Dana: den
- Dena
- Diaethylnitrosamin
- Diethylamine, n-nitroso
- Diethylnitrosamine

[more synonyms](#)

LAST UPDATED ON {MONTH DAY, YYYY}

Exhibit S

Welcome



Empowering a healthy tomorrow

SUMMARY, HIGHLIGHTS and TIMELINE of GENERAL CHAPTER <1469> NITROSAMINE IMPURITIES

By: Edmond Biba
Senior Scientific Liaison,
Science – General Chapters

Webinar
July 28, 2020



Background



Introduction

- ▶ Nitrosamines are common chemicals in water and foods including cured and grilled meats, dairy products and vegetables. Everyone is exposed to some level of nitrosamines.
- ▶ However, their presence in medicines, even at trace level is considered unacceptable because Nitrosamine impurities are probable human carcinogens.
- ▶ They are part of a group of high potency mutagenic carcinogens referred to as the “cohort of concern” in ICH M7. This “cohort of concern” comprises aflatoxin-like, N-nitroso- (functional group of nitrosamines), and alkyl-azoxy compounds

Exhibit T

Solco has designated Exhibit T as confidential. Plaintiffs hereby challenge that designation. In accordance with the Court's Confidentiality and Protective order, Plaintiffs will forward the Exhibit to the Court directly via email for its in camera review.